1999 Directory of Services and Yearbook 1997-1998 / Central Public Health Laboratory.

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PROTECTING THE POPULATION FROM INFECTION

PHLS

Central Public Health Laboratory

1999 Directory of Services and Yearbook 1997–1998

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A NATIONAL CENTRE FOR REFERENCE AND SPECIALIST MICROBIOLOGY

Design and Illustration: *Stewart McGregor, PHLS Headquarters*

The PHLS Central Public Health Laboratory, Colindale

Tel: 0181 200 4400

Director:
Professor SP Borriello
(Ext 3838)

Deputy Director:
Dr AC McCartney
(Ext 4942)

The Central Public Health Laboratory (CPHL) is the national centre for reference and specialist microbiology. CPHL provides specialist expertise and advice to the Area and Regional PHLS laboratories, NHS hospital laboratories, Consultants in Communicable Disease Control, community and hospital physicians, environmental health officers, government and industry. CPHL consists of four Divisions and within these Divisions there are specialist Reference Laboratories & Services.

CENTRAL PUBLIC HEALTH LABORATORY

Divisions & Laboratories

Research and Development

CPHL has a significant commitment to research and development. Much of this work involves the development of better tests for diagnosis of current and emerging infections, and development of molecular typing methods.

Reference Facilities

CPHL has facilities for many specialist tests. These include reference tests which are often complex or for micro-organisms rarely encountered in routine diagnostic laboratories. Traditional and molecular typing methods for distinguishing individual strains of microorganisms are also available and are invaluable in epidemiological investigations. CPHL has one of the few category 4 facilities in the UK.

Collaboration

There is close collaboration between CPHL and the rest of the Public Health Laboratory Service in all aspects of public health from investigation of outbreaks to surveys of the prevalence of new and existing human pathogens. There are also many links with relevant institutions in the UK and abroad eg NIBSC, Universities, CAMR, EU Laboratories, CDC (Atlanta USA).

Conference Facilities

CPHL has a lecture theatre seating 174 which has full projection and state of the art audiovisual facilities. In addition, there are two large well-equipped seminar rooms adjacent to the lecture theatre. Good cloakroom accommodation and catering facilities are available.

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Professor SP Borriello
Director

Dr AC McCartney
Deputy Director

Director's Foreword

The Central Public Health Laboratory is the major National Centre for Reference and Specialist microbiology in the UK, offering a service to England, Wales and the Channel Islands, and providing a significant proportion of such services for Scotland (within a recently finalised Service Level Agreement) and Northern Ireland. These services are underpinned by a strong research and development base, national resource collections such as the National Collection of Type Cultures and a continuing education and personal development programme. Our capability has been strengthened further by the recent appointments of Professor Eric Bolton as Director of the Food Hygiene Laboratory, and Dr David Livermore as Head of the Antibiotic Reference Unit, which this year is to become the Antibiotic Resistance Monitoring and Reference Laboratory. Training programmes and courses are also established for other professional bodies from the UK and abroad. We also provide advice to health professionals, government departments and industry.

Quality is an increasingly important consideration world-wide. We provide the National External Quality Assurance scheme for microbiology, a number of Food Microbiology External Quality Assurance Schemes, and Internal Quality controls for viral diagnostic tests. We also hold a contract with the Medical Devices Agency for evaluation of diagnostic kits for virology.

A recent important development was our establishment of the Association of Directors of European National Public Health/Hygiene Institutes. The inaugural meeting of this newly established forum was held at Colindale on 27th October 1998, and

The inaugural meeting of the Association of Directors of European National Public Health/Hygiene Institutes, Central Public Health Laboratory, October 1998.

had representatives from Italy, Finland, Sweden, Poland, Denmark, Athens, Czech Republic, Romania and Belfast. The primary purpose of this forum is to promote the effective collaboration within Europe of organisations with national responsibilities for reference and other specialist microbiology in order to enhance the protection of the people of Europe from infectious diseases.

The continuing threat of ever-present, emerging and re-emerging infectious diseases, coupled to creation of new opportunities for transmission by changing life-styles, new treatment procedures and climate change, and the erosion of public health programmes due to political upheaval and economic problems, poses a serious challenge to all those engaged in the control and prevention of communicable disease. On the other hand breath-taking developments in cellular and molecular biology and microbiology, the dawn of a new era in vaccinology, and developments in nanotechnology and communication, herald an age of exciting opportunities. The Central Public Health Laboratory looks forward to these opportunities and to the effective use of its resources in the continuing battle against disease.

Visitors to the CPHL

Mr Chris Kelly, Permanent Under Secretary for Health visited in June 1998. He was especially interested in a community outbreak of Hepatitis B Virus associated with an alternative therapy medical clinic in North London.

The Chairman of the Board, Sir Leslie Turnberg, visited CPHL in December 1997 for an overview of its work and discussions on its activities.

Visit of Professor RNM MacSween, President of the Royal College of Pathologists, November 1997.

Current Committee Membership

Professor SP Borriello:

Society of Microbial Ecology and Disease 1995-1997; (President).
Scientific Advisory Committee of the Edward Jenner Institute for Vaccine Research. Scientific Policy Advisory Committee for National Institute for Biological Standards and Control.
Scientific Advisory Board, Microscience Ltd.
Microbiol Ecology in Health and Disease. (Co-editor).
Bacteriology Volume, Topley and Wilson (Editor).
Editorial Board of: *Alpa Adria Microbiology; Eur.J. Clin Microbiol. Infect. Dis; J. Infect; Clin Infect Dis; Emerging Infect. Dis; Comm. Dis. Pulb. Hlth; Anaerobe.*

Dr AC McCartney:

Medicines Commission. Royal College of Pathologists: Speciality Advisory Committee on Microbiology, Examiner in Medical Microbiology; and Association of Clinical Microbiologists (Council Member). Health and Safety Commission: Health Services Advisory Committee - Working Group on Safe Working and the Prevention of Infection in Clinical Laboratories; and Working Group on: Safe Working and Prevention of Infection in Post-mortem rooms. Council for Science and Technology Institute - Health Care Scientific Advisory Committee.

Awards and Distinctions 1997-98

Professor SP Borriello:

Special Professor University of Nottingham

Visiting Professor LSHTM

Fellow of University College London

Publications 1997/98

Smith JA, Cooke DL, Hyde S, Borriello SP Long RG.
Clostridium difficile toxin A binding to human intestinal epithelial cells. *J. Med. Microbiol.* 1997; 46: 953-958.

Sussman M, Borriello SP Taylor DJ.
Gas gangrene and other clostridial infections In: Topley and Wilson's *Microbiology and Microbial Infections* 9th Edition; Bacterial Infections (Vol.3) Hausler WJ and Sussman M. Eds. Edward Arnold, London. p 669-91.

Powell NBL, Bishop K, Palmer HM, Ala'Aldeen DA, Gorringe AR, and Borriello SP.
Differential binding of apo and holo human transferrin to meningococci and co-localisation of the transferrin binding proteins (Tbp 1 and Tbp 2). *J. Med. Microbiol.* 1998; 47: 257-64.

Cooke DL and Borriello SP.
Non-specific binding of *Clostridium difficile* toxin A to murine immonglobulins is via the Fab component. *Infect. Immun.* 1998; 66: 1981-4.

Borriello SP.
Pathogenesis of *Clostridium difficile* infection of the gut. *J. Antimicrob. Chemother.* 1998; 41(Suppl C): 13-19.

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Clostridium difficile infections of the gut: the unaswered questions. *J. Antimicrob. Chemother.* 1998; 41(Suppl C): 67-9.

Logan RPH, Robins A, Turner GA, Cockayne A, Borriello SP, Hawkey CJ.
A novel flow cytometric assay for quantitating adherence of *Helicobacter pylori* to gastric epithelial cells. *J. Immunol Meth.* 1998; 213: 19-30.

Mahida YR, Galvin A, Mahk S, Hyde S, Sanfilippo L, Borriello SP, Sewell HF.
Effect of *Clostridium difficile* toxin A on human colonic lamina propria cells: early loss of macrophages followed by T cell apoptosis. *Infect Immun* 1998; 66: 5462-9.

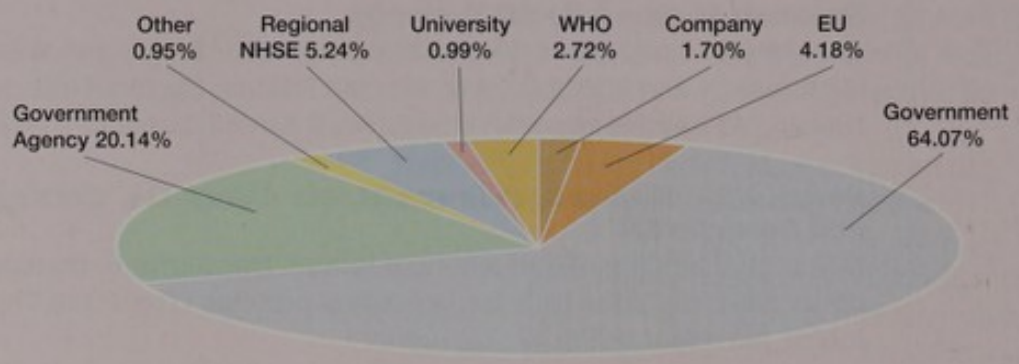
Sanfilippo L, Baldwin, TJ, Menozzi MG, Borriello SP, Mahida YR.
Heterogenicity in responses by primary adult human colonic epithelial cells to purified enterotoxin of *Bacteroides fragilis. Gut* 1998; 43: 651-5.

Bentley AH, Patel NB, Sudorczuk M, Loy P, Fulcher J, Dexter P, Richards J, Borriello SP, Zak KW, Thorn EM.
Multicentre evaluation of a commerical test for the rapid diagnosis of *Clostridium difficile* mediated antibiotic-associate diarrhoea. *Eur J Clin Microbiol Infect Dis.* 1998; 17:788-90.

Income and Publications

Research and Development activities at CPHL attract significant external grant funds. During the year 1997/98, a total of £1.8 million of new grant funds were awarded to CPHL. Analysis of the source of these grants by funding body is shown in the Pie Chart.

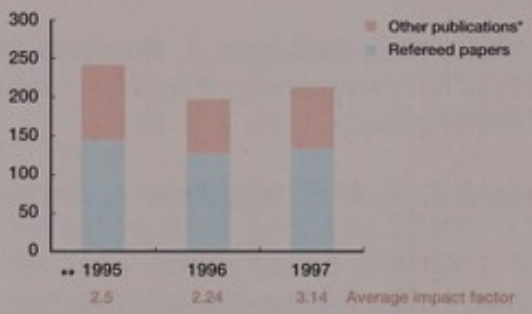
Analysis of Source of External R&D Grants by Funding Body 1997-98



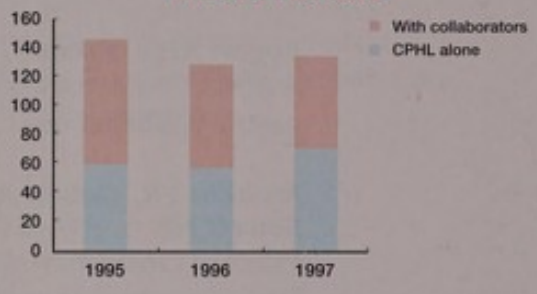
"Government" consists 90.57% Department of Health, 2.1% Home Office, 7.34% Ministry of Agriculture, Fisheries and Food.
"Government Agency" consists 100% Medical Devices Agency

Publications in Peer refereed journals have been maintained at about 150 per year for the three year period 1995 to 1997. Other publications averaged at about 50 per year over the same period. Details of publications for 1997-1998 can be found as part of the descriptions of Laboratories contained in this Yearbook. Science is increasingly a collaborative venture, and over half of all Peer reviewed publications are a result of such collaborations.

Publications



Publications in collaboration with other institutes



*Includes books, book chapters, book reviews, letters,abstracts and articles in unrefereed journals.

**Based on 96 papers in 1995, 85 in 1996 and 90 in 1997 which appeared in journals assigned an impact factor in the Journal Citation Reports database

Citation study of 1995 publications based on analysis of Scisearch database in June 1998.

No of papers with CPHL first author	No of cited papers	Total citations	Average citation rate	Maximun No of citation for any paper
91	65	523	5.75	70*

* **Reference:** Woodford N, Johnson A P, Morrison D, Speller D C E. *Current prospectives on glycopeptide resistance. Clin Microbiol Reviews* 1995; 8: 585-615.

Postgraduate education and training activities

CPHL is an affiliated Sponsoring Establishment for the Open University and has an active postgraduate group of 21 students, including three joint MRC studentships. The group meets regularly for seminar and teaching programmes covering academic, information technology and effective presentation skills. A postgraduate committee of five supervisors meets monthly to review student registrations, progress and examination arrangements and to identify training needs.

A number of CPHL staff, particularly Biomedical Scientists, are funded to attend day-release Master of Science courses. Other training activities in CPHL include regular microbiology and molecular microbiology seminars with internal and external speakers. A number of training courses are also organized ranging from microbiology for beginners to diagnostic methods for diphtheria for East European scientists. Recent courses for non scientific staff have covered subjects such as word processing and IT training, safety at work, and postal regulations for infectious agents.

CPHL Postgraduate Group

CPHL Postgraduate Group

L to R seated: Claire Jenkins, Fiona Clode, Henrik Chart (Sec), Tyrone Pitt (Chair), Mariya Afzal-Shah, Meeta Desai.

L to R standing: Janice Spencer, Richard Thwaites, Katrina Barlow, Rachel Hallett, Andrew Lawson, Alex Elliot, Jonathan Goulding, Andrew Vyse, Kathryn Harris, Joanne Stockton, Gioia Babini.

Students not in photograph:

Baharak Afshar, Nazim Chowdhury, Elliot Lawrence, Susana Pedraza-Diaz, Aruni de Zoyza, Anong Wongsriraksa.

Training Courses

CPHL educational activities for both PHLS and non-PHLS staff over the past year have included the following:

The Laboratory Diagnosis of Diphtheria	This course with its large practical component attracted participants from as far away as Canada, Greece and Slovenia and was held twice in 1997 -1998.
Transport of Infectious Substances by Air	Six sessions of the transport course (CAA approved under the Transport of Dangerous Goods Regulations) were held in Colindale and two in Scotland. Those attending represented a range of organisations including the PHLS, MRC, MAFF, the Veterinary Laboratory Agency and various medical schools and in addition to participants from the UK, delegates attended from the Gambia, the Channel Islands and Eire.
Clinical Pathology Internal Auditing	More than sixty people received practical training in audit as a result of this popular course. The organisers travelled to South Wales to accommodate staff requesting a more local venue.
Training in Food Spoilage	Sixty-eight PHLS staff attended two sessions of the food spoilage course which consisted of a series of talks supported by practical demonstrations in the Teaching Laboratory.
Quality Assurance for Gene Amplification Techniques in the Diagnosis of Infectious Diseases	Experts from as far afield at the Netherlands spoke at this meeting which was attended by over 80 scientists from the private and public sectors.
Food Associated Infections: An Update	This event attracted more than 100 representatives from over 50 local authorities as well as various laboratories.
Persistent Viral Infections: Their Diagnosis, Treatment and Prevention	One hundred and twelve were present at this symposium where topics ranged from molecular epidemiology to viruses in xenotransplantation.
New Insights Into Gastrointestinal Infections	On hundred and seventy attended. Delegates came from Eire, Pakistan, The Netherlands and Australia as well as the UK.
Changing Mucosal Flora and Disease	Another 170 microbiologists, including delegates from the USA, The Netherlands, Sweden, Norway, Finland, Denmark, Germany, Australia, Eire, Japan, China and Turkey, attended this two day meeting. A wide range of topics were covered relating to both specific organisms such as *Helicobacter pylori* and *Lactobacillus* and more general issues like normal gut flora, anaerobes, host defences and intestinal biofilms.
Intact Cell MALDI	This meeting dealt with a novel technique for rapid identification and attracted 100 delegates, some of whom came from the USA, Finland, Sweden and the Netherlands. This was the first scientific meeting to be held on a technique which requires only a single colony for an analysis which can be completed in a few minutes.

Future Activities and Further details:

These include a short course for infectious diseases clerks from local authorities and a course in gene amplification methods for diagnostic laboratories.

For further details contact:
Ms Rita Legros,
Education and Training Officer,
0181 200 4400, ext 3839.

Respiratory & Systemic Infection Laboratory

A WHO collaborating centre for diphtheria and streptococcal infections

Director's Foreword

Dr RC George

The PHLS Respiratory and Systemic Infection Laboratory (RSIL) is a national and international Reference Centre for a number of bacteria responsible for respiratory and systemic infections. We receive bacterial isolates and clinical samples from Public Health, National Health Service and commercial laboratories throughout the UK. The laboratory comprises two Units, the Streptococcus and Diphtheria Reference Unit and the Atypical Pneumonia Unit. The first of these units is a WHO Collaborating Centre and as such provides laboratory and advisory support for national and other centres world-wide.

During 1997/98 a total of 14,622 reference specimens and samples were received and reported upon. This represents a 10% increase over the total for 1996/97 of 13,279 which, in turn was a 12% increase over the 1995/96 total. A listing of the reference services provided by RSIL is given overleaf. The steady increase in reference testing referrals is a reflection of the utility of RSIL's results to our customers and their general satisfaction with the work we do. We also provided testing (830 samples and specimens) and advisory services to PHLS and NHS Laboratories and Consultants in Communicable Disease Control (CsCDC) in the investigation of 87 outbreaks of infection within our remit.

In addition to reference testing the laboratory also undertakes Research and Development work in accordance with priorities established by the PHLS Overview of Communicable Disease. Continuing increases in reference workload and the requirement to undertake outbreak investigations as and when they arise has restricted the amount of core-funded staff time that can be devoted to Research and Development. This is regrettable but unavoidable. It has certainly stimulated senior staff to seek external funding at every opportunity and the number of grant applications submitted has notably increased.

Systems and organism-based expertise developed through provision of reference services contributes to the identification of new areas of Research and Development opportunity which may, in time, determine the need and scope of new reference or surveillance activities. For example, a PhD thesis project on bartonellae has eventually led to the establishment of a referred service for the diagnosis of infections due to these organisms. Similarly, we are at present embarking upon work to test the hypothesis that *Bordetella pertussis* infections are significantly under-diagnosed in all age groups and that current surveillance strategies may be inadequate.

Reference And Diagnostic Testing Services

Epidemiological typing of Lancefield group A streptococci (*S. pyogenes*)

Epidemiological typing of Lancefield group B streptococci (*S.agalactiae*)

Epidemiological typing of Lancefield group C and G streptococci

Epidemiological typing of pneumococci (*S. pneumoniae)*

Identification of streptococci and related genera

Identification and toxigenicity testing of *Corynebacterium diphtheriae*

Diphtheria Immunity/Vaccination studies

Tetanus Serology

***Legionella pneumophila* serology**

***Legionella pneumophila* urinary antigen ELISA**

Legionella cultures for identification/typing

Respiratory samples for legionella diagnosis

***Mycoplasma pneumoniae* serology**

Clinical samples for mycoplasma culture/identification/PCR

***Chlamydia* spp serology**

***Chlamydia* spp PCR**

Bartonella (Cat Scratch Disease) serology

Bartonella PCR

Public Health:

Invasive Group A Streptococcal Disease In England & Wales

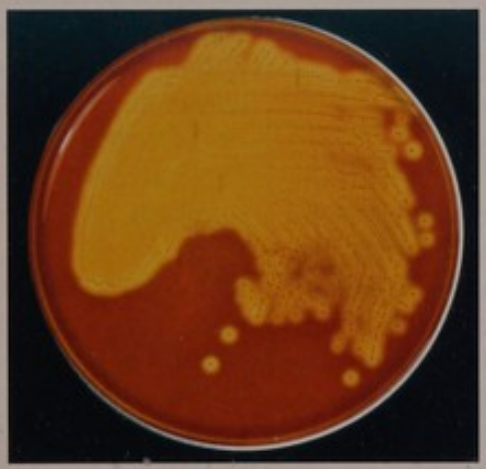
During the late 1980s and the early 1990s, numerous reports have documented changes in the epidemiology of diseases caused by group A streptococci (GAS) and an increase in virulence particularly, in Northern Europe and North America. Such changes have been noted amongst previously healthy individuals as well as in those with predisposing conditions such as immunosuppression, myelomas and varicella. Understanding these changes in epidemiology and virulence is important for recognition and control of infection and also for gaining valuable information concerning pathogenesis. GAS elaborate a range of surface virulence determinants and extracellular products, for example the M protein. Since the M protein cell surface antigen is one of the major virulence factors of GAS and some M types have been linked to specific clinical diseases, the changing epidemiology may be related directly to a changing distribution of serotypes.

Following the cluster of cases of GAS necrotising fasciitis in Gloucestershire in 1994, the PHLS initiated a three-year programme of enhanced clinical, microbiological and epidemiological surveillance of all invasive GAS disease in England and Wales. The main objectives of the surveillance were to detect outbreaks or clusters in a timely manner, to determine the trend in the overall number of cases; to determine patterns of M types and virulence factors, and also to determine the clinical manifestation of, and risk factors for, invasive GAS infection. This was completed at the end of June 1997 and the dataset is currently being analysed. Interim reports have been published in the PHLS Communicable Disease Report and presentations made at national and international conferences. Clinical microbiologists and CsCDC have found these data of great use in guiding their clinical and public health response to individual cases and also clusters of invasive GAS infection both in the community and hospital.

During the surveillance period, more than 2000 non-duplicate GAS isolates from confirmed cases of invasive GAS disease in England and Wales have been received by the PHLS Streptococcus and Diphtheria Reference Unit for serotyping. The overall mortality rate

Right

Streptococcus pyogenes (Lancefield group A streptococcus) on blood agar medium



amongst these patients was high at 27%, with a much higher fatality rate amongst the elderly (mortality rate over 65 years of age was 40%). The disease incidence rates per 100,000 of the population during 1996 varied with age from 0.84 (males) and 1.00 (females) in those aged 0-10 years, to 7.74 (males) and 5.15 (females) in those aged >80 years. Associated morbidity was also significant, for example, 23% of all patients required some form of therapeutic surgical intervention and 19% were admitted to intensive care units. Forty different M types were isolated. M1, M3 and R28 were the most common, representing 60% of the total. Infection with M types 1 or 3 (regarded as more virulent types) was associated with mortality of 36% and 39% respectively, whilst for R28, the mortality rate was 17%. In addition, during the three-year period, ten clusters of invasive GAS disease were noted in various geographic areas of England and Wales.

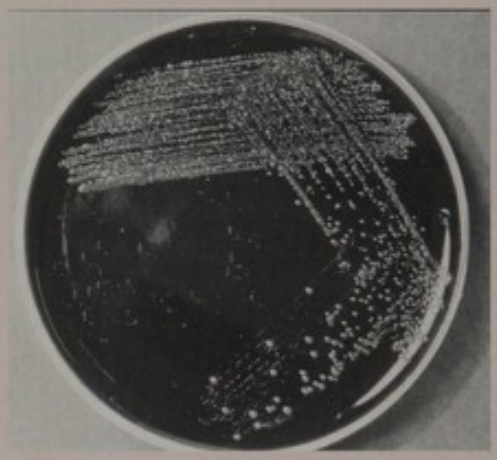
The data from this surveillance emphasise the high morbidity and significant health care provider costs of invasive GAS infections and will help to inform therapeutic and preventative strategies for GAS disease.

Research and Development

A Pilot Study to Investigate the Role of PCR in the Diagnosis of Pertussis Infection in the UK

Although pertussis appears to be a well-controlled disease in the UK, a substantial resurgence of this vaccine-preventable infection has been noted recently in North America, Australia and some European countries. This is exemplified by the 1996 pertussis epidemic in The Netherlands, which showed an incidence fivefold higher than in previous years. Within these resurgences infections in older children, young adults and those who have been vaccinated accounted for a substantial proportion of the cases. Waning vaccine immunity, variation in vaccine quality, decrease in vaccine coverage and possible emergence of new pertussis strains have all been postulated as possible mechanisms.

The traditional approach to the laboratory diagnosis of pertussis is culture and isolation of the causative agent *Bordetella pertussis*. However isolation of this organism is difficult and



Bordetella pertussis
on CHC (charcoal agar with cephalexin) after incubation for 5 days at 37°C with 5% $C0_2$

this approach lacks sensitivity, particularly when mild or atypical symptoms are present, or when the patient has received antibiotics prior to the investigation. Estimates of the sensitivity range from 6 - 60%. An alternative approach is to use the polymerase chain reaction (PCR) which allows detection of viable, dying or dead organisms even when present in the clinical sample in extremely small numbers.

RSIL, in collaboration with several partners, but principally with the Immunisation Division of the PHLS Communicable Disease Surveillance Centre (CDSC), undertook a pilot project to develop/evaluate PCR methods for use in enhanced surveillance studies. The PCR method used targets the pertussis toxin promoter region and, in

our hands, is capable of detecting *ca* 10 organisms per test reaction (10^2/mL). After the incorporation of both an internal positive control and a DNA extraction control (a PCR directed against the human mitochondrial cytochrome oxidase gene), we used this PCR in two studies. In the first we examined pernasal swabs from 138 patients, who had symptoms suggestive of pertussis infection, obtained from one General Practitioner. Of these nine (6.5%) were positive by PCR but only one was positive by culture. Sera were available from ten of the 138 patients and were examined by a battery of serological assays. Of these three had serological evidence of pertussis and all of these were PCR positive. Although the numbers are very small this suggests good concordance between the two methods.

In the second study, undertaken with the Queen's Medical Centre (QMC), Nottingham, the PCR was used in a prospective study of the aetiology of community acquired pneumonia in children. The study was prompted by the results of an audit which indicated that investigation and management of children admitted to QMC with pneumonia was very variable with the least useful investigations being used most frequently and the most useful being used least. Overall the study found evidence of infection in 47/89 children, 11 of these being caused by *B.pertussis*.

From the results of our own pilot studies, and the experience of others, it would appear that ascertainment of pertussis by conventional methods is very poor. The application of DNA amplification techniques to pertussis diagnosis should allow a clear definition of the true incidence in all age groups and the burden of morbidity imposed. RSIL and the Immunisation Division of CDSC intend to extend these studies further by examining a substantial number of specimens from a wide range of geographical sources in the UK.

Committee Membership

Dr RC George:	International Pneumococcal Molecular Epidemiology Network
	Adult and Travel Immunisation Panels of DoH Joint Committee on Vaccines and Immunisation
Dr T Harrison:	European Working Group on Legionella Infection
Dr A Efstratiou:	European Laboratory Working Group on Diphtheria (Co-ordinator)
	Editorial Board, Journal of Medical Microbiology
Dr D Pitcher:	Advisory Group on the Taxonomy of Mycoplasmas to the International Committee on Bacterial Systematics

Awards And Distinctions

Dr R George:	Adviser to WHO on diphtheria, streptococcal infection and antibiotic resistance surveillance
	External Examiner: MSc in Medical Microbiology, LSHTM, 1995,1996 and 1997.
	Honorary President: British Society for Microbial Technology
Dr A Efstratiou:	Adviser to WHO on diphtheria and streptococcal infection

Current Grants

Efstratiou A.
Microbiological Surveillance of Diphtheria in Europe.
DGX11 BioMed - European Commission, 225,000 ECU, 1998-2001.

Efstratiou A.
Microbiological Surveillance of Diphtheria in Eastern Europe.
Inco Copernicus - European Commission, 230,000 ECU, 1998-2001.

George RC.
Antimicrobial susceptibility testing of toxigenic and non-toxigenic *C. diphtheriae* isolates. Roussel/UCLAF, £11,000,1997-1998.

George RC, Hall LMC (London Hospital Medical College).
DNA-based methods for serotype discrimination in *Streptococcus pneumoniae*.
MRC Collaborative Studentship - One third of student's time in RSIL,1997-2000.

George RC, Miller E.
Enhanced laboratory diagnosis of pertussis in the UK. Manufacturers of Pertussis Vaccines, £56,000, 1998-2000

Harrison TG, Joseph C plus other colleagues from PHLS CDSC.
European Surveillance of Legionnaires' Disease. DGV European Commission, 110,000 ECU (RSIL component), 1998-2000.

Harrison TG, Grundmann H plus other colleagues from PHLS Trent.
Investigations to determine the feasibility of electronic transmission and comparison of digital typing data for *Legionella pneumophila*. PHLS R&D Fund. £4,100, 1998-1999

Pitcher D, Miles R (Kings College Hospital).
Genetic and biochemical analysis of *Mycoplasma fermentans* strains in relation to isolation site and human disease. MRC Collaborative Studentship - One third of student's time in RSIL, 1997-2000.

Publications 1997/98

Barnham M, Weightman N, Chapman S, Efstratiou A, George RC, Stanley J.
Two clusters of invasive *Streptococcus pyogenes* infection in England and Wales. *Adv Exp Med Biol* 1997;418:67-9.

Colman G, Cooke EM, Cookson BD, Cooper PG, Efstratiou A, George RC.
Pneumococci causing invasive disease in Britain 1982-1990. *J Med Microbiol* 1998;47:17-27.

Desai M, Tanna A, Efstratiou A, George R, Clewley J, Stanley J.
Extensive genetic diversity among clinical isolates of *Streptococcus pyogenes* serotype M5. *Microbiol* 1998;144:629-37.

Efstratiou A, Engler KH, De Zoysa A.
Diagnosis and epidemiology of diphtheria. In: *Molecular Bacteriology: Protocols and Clinical Applications.* Eds. Woodford N, Johnson AP. *Methods in Molecular Medicine series No. 15.* Totowa, Humana Press Inc. 1998, p191-212

Efstratiou A, George RC, Gaworzewska ET, Hallas G, Blake W, Monnickendam MA, McEvoy M.
Group A streptococcal invasive disease in England and Wales. *Adv Exp Med Biol* 1997;418:207-10.

Efstratiou A, George RC, Tanna A, Hookey JV, Caugant D, Holm SE, Kriz P, Martin D, Upton M, Cartwright KV.
Characterisation of group A streptococci from necrotising fasciitis cases in Gloucestershire. *Adv Exp Med Biol* 1997;418:91-3.

Efstratiou A.
Pyogenic streptococci of Lancefield groups C and G as pathogens in man. *J Appl Bacteriol* 1997;83:72S-79S.

Efstratiou A.
The European Laboratory Working Group on Diphtheria. Strengthening disease surveillance and support of networks. Expanded Programme on Immunization. Seventh Meeting of National Programme Managers. Working Paper, World Health Organization, European Regional Office, 1997, CMDS 01 01 04/14.

Fry NK, Harrison TG.
An evaluation of intragenic rRNA gene sequence length polymorphism for the *Legionella* spp. *J Med Microbiol* 1998;47:667-78.

Fry NK, Harrison TG.
Diagnosis and epidemiology of infections caused by *Legionella* spp. In: *Molecular Bacteriology: Protocols and Clinical applications.* Eds: Woodford N, Johnson AP. *Methods in Molecular Medicine series No. 15.* Totowa, Humana Press Inc. 1998, p213 –42.

Funke G, Efstratiou A, Kuklinska D, Hutson RA, De Zoysa A, Engler KH, Collins MD.
Corynebacterium imitans sp. nov. isolated from patients with suspected diphtheria. *J Clin Microbiol* 1997;35:1978-83.

George RC, Johnson AP, Speller DCE, Efstratiou A, Broughton K, Patel BC.
Serogroups/types and antibiotic resistance of referred isolates of *Streptococcus pneumoniae*: 1993-1995. *Commun Dis Rep CDR Rev*, 1997;7:R153-9.

George RC.
Diphtheria. *Medicine*, 1997;25:8-10.

George RC.
The impact of molecular methods on clinical bacteriology. In: *Molecular Bacteriology: Protocols and Clinical applications.* Eds: Woodford N, Johnson AP. *Methods in Molecular Medicine series No. 15.* Totowa, Humana Press Inc. 1998 p1-15.

Gillespie SH, McHugh TD, Ayres H, Dickens A, Efstratiou A, Whiting GC.
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The Laboratory of Hospital Infection

A WHO nosocomial reference centre and a WHO staphylococcal reference centre.

Director's Foreword

Dr B Cookson

The Laboratory of Hospital Infection (LHI) comprises an Epidemiological Typing unit, an Infection Control unit and an Antibiotic Reference unit. In 1996, LHI became the first accredited hospital infection reference laboratory in the world. Its staff provide advisory and reference services to many types of health care workers, governmental and EU bodies and other parties involved in hospital and, with the recent changes in the delivery of health care, many community acquired infections.

We receive bacterial isolates and serological samples from Public Health, National Health and commercial laboratories throughout the UK. In 1997-98 we processed and reported upon more than 60,000 specimens and samples, the numbers increasing by *ca* 15% per year since 1993 for non-staphylococcal and by *ca* 30% per year for staphylococcal specimens. The large range of services we provide are outlined below. The increase in numbers reflects the high profile of hospital infection and the emergence and spread of antibiotic resistant organisms, along with the general satisfaction in the turnaround times and quality of our service.

The Laboratory has a wide remit and provides a comprehensive microbial typing service. It performs surveys of the occurrence of most nosocomial pathogens and links with other typing networks or systems that enable us to monitor the national and international spread of these organisms. We advise infection control teams (ICTs), health care workers and the Department of Health on the prevention and control of infection, including the management of outbreaks and the appropriate use of antibiotics and disinfectants. We have a major committment to the education of ICTs and have interacted with others to establish diplomas in Infection Control that are now attracting international interest. We also provide advice and support on-site when necessary using established, or develop new, tools to investigate the reservoirs and sources of hospital infection.

We have a particular interest in exploring ways in which infection control and antibiotic prescribing control strategies can limit the rise of antibiotic resistance. We examine the quality of antimicrobial susceptibility testing (with the CPHL-based NEQAS system), devise surveillance strategies, establish networks and are involved in many aspects of policy design, audit and review cycles. Finally, we assist in the design, and help perform, projects with our customers, further our relationships with international and national bodies involved in infection control and antibiotic therapy, and perform other research and development in all aspects of our work.

Identification and epidemiological typing of:

- staphylococci
- enterococci
- gram-negative rods, in particular -
  - *Klebsiella* spp.
  - *Enterobacter* spp.
  - *Serratia* spp.
  - *Pseudomonas* spp.
  - *Stenotrophomonas maltophilia*
  - *Burkholderia* spp. (especially *B. cepacia* and *B. pseudomallei)*
  - *Acinetobacter* spp.

Antimicrobial testing for epidemiological and therapeutic purposes at the phenotypic and genetic level.

Serodiagnosis tests for infections caused by:

- *Staphylococcus aureus*
- *Streptococcus pyogenes*
- *Pseudomonas aeruginosa*
- *B. pseudomallei*

Infection control, surveillance, audit and antimicrobial advice

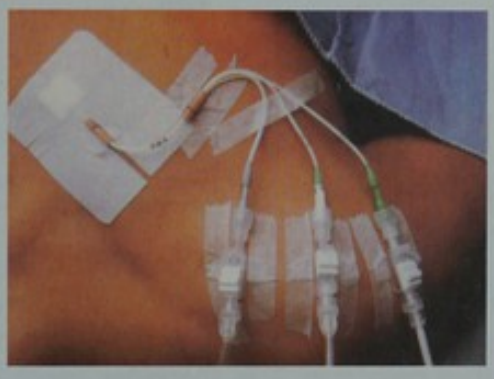
Public Health:

Surveillance, cost and audit of hospital infection

LHI has been involved in two National UK Prevalence surveys in 1980 and 1993. Although the rates of infection were comparable (*ca* 10%), their nature was very different, with larger numbers of device-related infection probably due to the increasing use of invasive techniques, and decreased numbers of surgical infections related to the ever-shortening lengths of hospital stay and increased use of day-care surgery. We have conducted pioneering research into the validation of surveillance methodologies and are currently validating an optimal method of post-discharge surveillance for surgical wound infection. We are soon to publish the most extensive study yet conducted into the costing of nosocomial infection, examining the direct, indirect and intangible costs of these infections. A similar study has just been completed looking at the costing of day-care surgery infections.

Right

Multi-lumen central vascular device in an immunocompromised patient



Our most ambitious project to date has been the Clinical Audit Project of hospital infection control activities in 19 hospitals in England and Wales. This identified the need for changes in surveillance methodologies and improving the information technological interface between the hospital infection and the patient information systems and the overwhelming importance (a seven-fold increase in infection risk) in hospital infection from urinary and intravenous catheters. During the course of the study, infection control and antibiotic prescribing policies were analysed. Data were also collected on teaching practices and observational audits of common infection control procedures. These were fedback to multi-disciplinary teams of heath-care workers convened from participants and used to derive "bottom-up" infection control consensus guidelines. These are amongst the most requested publications of the PHLS, and are intended to be developed locally by UK hospitals. Their acceptability will also be explored in other EU countries in a DGXII EU funded project ("HARMONY").

Antibiotic resistance in nosocomial pathogens

The emergence of antibiotic resistance in nosocomial pathogens has caught the attention of the media and is now one of the major UK Public Health challenges of the 1990s. LHI has done much to monitor the emergence of methicillin-resistant *Staphylococcus aureus* (MRSA), glycopeptide resistant enterococci (GRE) and multiple-resistant gram-negative rods (GNRs) over the last few years.

MRSA have probably received the highest priority, although GRE and GNRs are usually more difficult to treat. LHI

workloads have increased from *ca* 12,000 in 1990 (*ca* 50% MRSA) to 43,000 in 1997-98 (*ca* 85% MRSA). We have described the evolution of epidemic MRSA (EMRSA) spreading between hospitals and played a major role in writing all three MRSA control working party documents and another that has described control strategies in nursing homes. The 1990s heralded the emergence of new "supra-regional" strains (EMRSA-15 and 16) which have a particular propensity for spread. This has been further encour-aged by changes in health care delivery e.g. increasing inter-ward transfers, decreasing lengths of hospital stay, reducing the effectiveness of alert organism surveillance. In a univariate analysis of an LHI ICT questionnaire survey, the importance of early MRSA detection, mupirocin resistance and the "endemic" problem of constant challenges with MRSA was apparent.

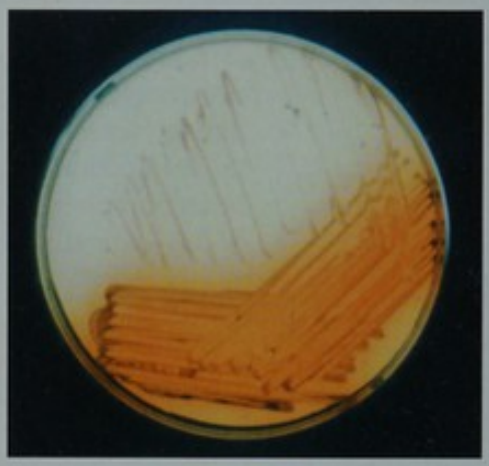
We have shown that the proportions of MRSA relative to all *S.aureus* bacteraemias has increased from <2% in 1989 to nearly 32% in 1997. Data from the 1993 National Prevalence Survey found that MRSA colonisation was the major risk factor for hospital acquired infection, causing 6.6% of all hospital acquired infections and 28% of those due to *S.aureus*. MRSA caused between 24 and 54% of all *S.aureus* infections in our Clinical Audit project.

LHI has led an International experimental phage typing MRSA study and has been very active in developing DNA typing systems, including two international inter-centre stand-ardisation studies. More recently, several PCR-based typing systems have been developed and we are also assessing some rapid MRSA detection systems that will increase the speed of detection of MRSA in hospitals.

Research and Development

Transmissibility of *Burkholderia cepacia* in Cystic Fibrosis

Cystic fibrosis (CF) is a disease characterized by malabsorption, malnutrition and chronic bronch-opulmonary infection. These are clini-cal manifestations of the abnormal transport of ions across mucosal surfaces and this affects mainly the sweat glands, pancreas, gut and respiratory tree. It is the impairment of the respiratory tract function that contributes most to the high morbidity and mortality of CF patients. The range of microbes associated with respiratory infection in CF is limited and the great majority become infected with the opportunist pathogen *Pseudomonas aeruginosa*. However, in the last 15 years the plant pathogen *Burkholderia cepacia*, which causes rot in onions, has emerged in the CF community as the



Highly transmissible strain of *Burkholderia cepacia* from a cystic fibrosis patient

cause of an abrupt serious deterioration in health, and even death, in about one-third of patients who contract it. There is therefore great concern among CF pa-tients and their carers and interest in ways of reducing the risk of transmission.

We carried out a survey funded by the Cystic Fibrosis Trust of 16 major CF treatment centres in the UK and showed that of 180 patients with *B. cepacia*, about 70% were colonised/infected by different strains as judged by their DNA fingerprints. However, the remainder harboured a highly transmissible strain which had most probably originated from an outbreak in Toronto, Canada and had been introduced into the UK CF population through holiday exchange visits to Canada. This "epidemic" strain was isolated from 10 different centres and in some centres was recovered from all *B. cepacia*-positive patients. Further it became clear that those centres which segregated patients for treatment on the basis of whether they were colonised with *B. cepacia* had fewer new acquisitons of the organism among their patients. The Cystic Fibrosis Trust now advises patients of the risk of contracting *B. cepacia* which varies from low for casual meetings to high for sharing eating and drinking utensils, sibling contacts, and receiving physiotherapy together. Recently, at least three "epidemicity factors" have been identified and we have found them to be almost exclusively associated with transmissible strains. To this end the laboratory provides a PCR assay service to CF physicians to confirm whether particular patients are colonised by transmissible strains of *B. cepacia* and gives advice on segregation of patients and infection control practices.

Committee Membership

Dr B Cookson:

Hospital Infection Society and Infection Control Nurses Association (ICNA) Working Party (HIS WP) on Vancomycin resistant enterococci (Chairman)
Advisory Committee for the Diploma of Hospital Infection Control (Secretary)
Hospital Infection Society representative on BSI CH/67 sterilisation of medical devices
Association of Medical Microbiologists Clinical Services Sub-Committee
Member of the Hospital Infection Society (HIS) Council
HIS WP on handwashing and the HIS/ICNA/DH handwashing liaison group
Joint British Society of Antimicrobial Chemotherapy, ICNA and HIS MRSA working parties
Steering Group HELICS II (DGV) (UK Co-ordinator)
Executive Committee of the European Society of Clinical Microbiology Working Groups on Bacterial Epidemiological Markers and the European Study Group of Nosocomial Infection
IUMS International Committee of phage typing of staphylococci
European Council examining standards in infection control (UK Representative)

Editorial Board of:
- Journal of Hospital Infection
- Microbial Drug Resistance
- The Infectious Disease Review

Dr T Pitt:

Serious Hazards of Transfusion (PHLS/NBA) Working Party
National Melioidosis Group
Steering Group NBA/PHLS study on bacterial contamination and bone banking

Editorial Board of:
- Journal of Hospital Infection (Assistant Editor)
- Medical Microbial Letters
- European Journal of Clinical Microbiology and Infectious Disease
- Journal of Infectious Diseases and Antimicrobial Agents (Thailand)

Dr D Livermore:	British Society of Antimicrobial Chemotherapy Council National Health Executive Sub-Committee on Antimicrobial Resistance Editorial Board of: Journal of Medical Microbiology (Editor) Journal of Antimicrobial Chemotherapy and Antimicrobial Agents and Chemotherapy
Miss L Taylor:	Central Sterilising Club Executive Committee Steering Group of DH Funded Guidelines in Infection Control Study European Council examining standards in infection control (UK Representative) Special Interest Group, Care Sector Consortium Medical and Surgical Products Users Liaison Group
Mr P Hoffman:	Advisory Committee to the DipHIC British Standards Institution disinfection technical committee CH/57 *ad-hoc* WHO/CDC Working Group to assess jet injectors NHS Estates Business Agency theatre linen specifications working party Central Sterilising Club working parties on *Reuse of single-use items* and *Good practice for fabric laundering*
Dr N Woodford:	Editorial Board of: Journal Antimicrobial Chemotherapy (Assistant Editor)

Awards and Distinctions

Dr B Cookson:	Honorary Senior Lecturer Royal Free Hospital External Examiner for MSc at the London School of Hygiene and Tropical Medicine Examination Committee for the Diploma of Hospital Infection Control (Secretary) WHO Consultant and Advisor to the Scientific Working Group on Monitoring and Management of Bacterial Resistance to Antimicrobial Agents Advisor to the WHO/EU/USA Task Force on Antibiotic Resistance Surveillance Advisor to the WHO on Nosocomial Infection Surveillance Member of the Advisory Board of the Portuguese National Network on tracking of antibiotic resistant organisms
Dr T Pitt:	Honorary Senior Lecturer at the Brompton Hospital and the London School of Hygiene and Tropical Medicine External Examiner of MSc Modules Westminster College, University of London

Dr D Livermore:	Honorary Senior Lecturer St Bartholomews and the Royal London Trust hospitals Member of Antibiotic Susceptibility Working Party of the British Society of Antimicrobial Chemotherapy
Ms L Taylor:	Consultant Nurse Advisor to the Chief Nursing Officer for England Examiner at the Royal Institute of Public Health and Hygiene Certificate in Hospital and General Hygiene Associate Lecturer, Royal College of Nursing Institute (College of the University of Manchester). Consultant Nurse Advisor to the Ministry of Health, Lisbon

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Nosocomial Infection Surveillance Unit

The current primary activity of the Unit is the establishment of a Nosocomial Infection National Surveillance Scheme (NINSS)

What is NINSS?

The Nosocomial Infection National Surveillance Scheme (NINSS) was launched in March 1996 to assist hospitals and clinicians monitor hospital-acquired infection (HAI) and to develop a system for intra and inter-hospital comparison of rates.

Nosocomial Infection Surveillance Unit staff

NINSS Aims and Objectives

The aims of NINSS are to provide hospitals with estimates of rates and risk of HAI so that they can compare the incidence of infection in their own hospital year on year with aggregated, anonymised data from other participating hospitals. The results can be used as a clinical audit tool and benchmark to enable clinicians and managers to assess the quality of health care in their hospital. A key objective of NINSS is to identify where infection rates are high so that resources can be targeted at those areas. To achieve these goals NINSS has developed surveillance protocols targeted at specific types of HAI: initially hospital-acquired bacteraemia and surgical site infection. Workload for infection control personnel and the NINSS team is reduced substantially by using an optical mark recognition system for data collection, now enabling the NINSS team to feed back the results in eight weeks or less. Surveillance information is designed for action. This is achieved by each hospital interacting with the multi-disciplinary team at NINSS who are available to give advice on ways to improve patient care by reducing the risks of HAI.

Progress Report

Since the launch in 1996 over 160 hospitals (67% of all hospitals) have registered an interest in joining and 110 participants have completed one or more periods of surveillance (participation rate of 45%).

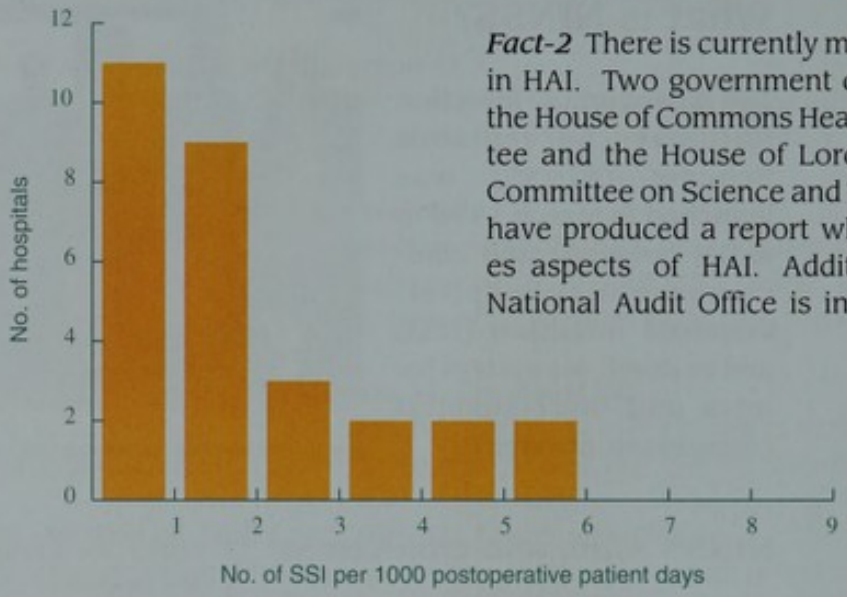
During the first year of established surveillance 58 hospitals have participated in the development of an innovative protocol for the surveillance of hospital acquired bacteraemia and the identification of associated risk factors and 73 hospitals have received quarterly reports of their surveillance of surgical site infections.

A typical example of some of the results contained in the quarterly surgical site infection (SSI) reports is shown in the figure below. This illustrates the

distribution of surgical site infection rates in the hip prosthesis category of surgical pro-cedures and enables hospitals to identify their position in relation to other participating hospitals.

Right

Hip prosthesis
Distribution of SSI rates per 1000 postoperative patient-days



The next modules to be developed are for the surveillance of urinary tract infection and identification of critical infections in patients admitted to intensive care units. Further information about NINSS can be obtained from NISU staff.

Fact-1 Hospital-acquired infections (HAI) are an unwanted outcome of hospital admission and are an important cause of morbidity and mortality. At any one time, about one in ten patients will be suffering from an infection which they have acquired in hospital. The costs to the NHS have been estimated to be £110 million annually[1]. The average increase in length of stay for surgical patients who develop an infection, estimated as 8.2 days[2] also affects waiting lists for admission to hospital.

Fact-2 There is currently much interest in HAI. Two government committees, the House of Commons Health Committee and the House of Lords Standing Committee on Science and Technology, have produced a report which includes aspects of HAI. Additionally, the National Audit Office is in the process of undertaking a Value for Money investigation on the management of infection control in acute hospitals.

Fact-3 There is evidence to suggest that up to one third of HAI could be prevented by an infection control programme that includes surveillance activity, with feedback of information to clinical staff[3]. It is intended that NISU will contribute to the prevention of HAI by facilitating the collection and use of surveillance data by hospitals in England.

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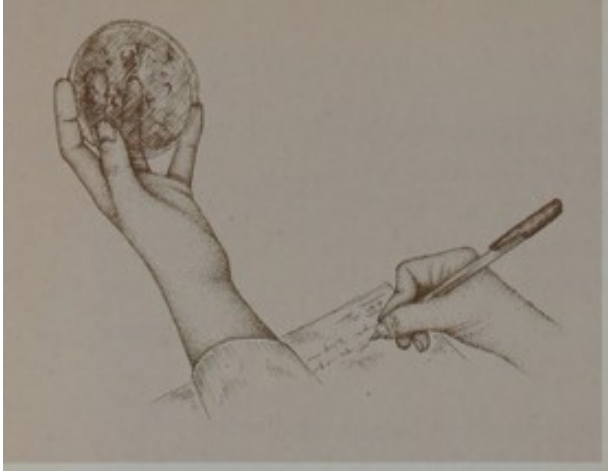
Committee Membership

Dr AD Pearson:	Chairman Joint Department of Health and PHLS Nosocomial Infection National Surveillance Scheme (NINSS) Management Group
Mrs J Wilson:	Department of Health Advisory Group on Hepatitis
	Education Sub-committee, Infection Control Nurses Association
	Handwashing Liaison Group (HIS/ICNA/PHLS/DH)
Mrs J Sedgwick:	Infection Control Nursing Advisor to HealthProm
	Executive Committee of HealthProm (registered charity involved in medical education in the former Soviet Union)

Awards And Distinctions

Dr AD Pearson:	Adjunct Professor of Microbiology, University of Maryland Biotechnology Institute, Maryland USA
	Honorary Senior Lecturer in Medicine, United Medical and Dental School (UMDS) London.
Mrs J Wilson:	External Examiner, University of Hertfordshire
	Curriculum development team (diploma and degree level courses in infection control), University of Hertfordshire
Publications:	See Laboratory of Hospital Infection



Laboratory of Enteric Pathogens

A WHO collaborating centre for phage typing and drug resistance.

Acting Director's Foreword

Dr H Smith

The PHLS Laboratory of Enteric Pathogens (LEP) is the National Reference Centre for England and Wales for pathogenic enteric bacteria. The LEP receives bacterial isolates, and clinical specimens, as faeces and sera, from Public Health, National Health Service and other laboratories throughout the UK, including commercial laboratories serving medical, veterinary, food and water industry customers. The Laboratory is the co-ordinating laboratory centre for the European Union- funded Enter-net project. The LEP comprises six laboratory units and provides reference services for *Campylobacter* spp. *Escherichia coli, Shigella* spp. and related organisms, *Helicobacter* spp. and *Salmonella* spp. The work of the LEP research also covers antibiotic resistance and molecular epidemiology, and a range of projects which are mainly externally funded.

During 1997/98 the reference workload was 66,412, a 19% increase compared with 1996/97. Part of the increase resulted from the introduction of a reference service for campylobacters. However there were also increases in referrals of *Salmonella* spp., particularly *S. enteritidis*, and Vero cytotoxin-producing *E. coli* O157. A list of the reference services provided by the LEP is shown overleaf.

The Research and Development programme within the Laboratory concentrates on the priority areas laid down by the PHLS Overview of Communicable Disease. Projects are aimed at improving the identification of enteric pathogens, the diagnosis of infection and techniques for bacterial characterisation Studies on antimicrobial resistance are given a high priority. The other part of the R & D programme comprises projects on pathogenic mechanisms in enteric pathogens. Much of the R & D programme is funded by external grants and details of current grants are included on page 43.

1997 was a very significant year for the LEP because Dr Bernard Rowe retired as Director in December in that year. Dr Rowe joined the PHLS in 1968, and in 1978 was appointed the first Director of the then recently formed Division (later Laboratory) of Enteric Pathogens. Over these 30 years Dr Rowe has made a tremendous contribution to the study of bacterial gastrointestinal infections both nationally and internationally, and this was recognised in the New Year Honours when he was awarded the Order of the British Empire for services to the surveillance of foodborne illnesses. Early in 1998 Dr Rowe returned to CPHL on a part-time basis to be the first Chairman of the newly-formed Division of Gastrointestinal Infections, which encompasses the LEP and the Food Hygiene Laboratory. This reorganisation will enable a more co-ordinated approach to activities on gastrointestinal infections.

Reference And Diagnostic Testing Services

Identification and serotyping of *Salmonella* spp.

Phage typing of *Salmonella* spp.

DNA-based typing of *Salmonella* spp.

Serodiagnosis of S. *typhi* and *S. paratyphi* infection

Identification and serotyping of *E. coli*

Identification of enterovirulent *E. coli*

Phage typing, VT typing, and DNA-based typing of *E. coli* O157

Serodiagnosis of *E. coli* O157 infection

Isolation of VTEC and other enterovirulent *E. coli*

Identification and serotyping of *Shigella* spp.

Phage typing of *Sh. sonnei*

DNA-based typing of *Shigella* spp.

Identification and serotyping of *Vibrio spp.*,phage typing of *V. cholerae* O1

Identification and serotyping of *Yersinia* spp.

Serodiagnosis of *Yersinia* spp. infection*

Identification of other members of the Enterobacteriaceae**

Identification of *Campylobacter* spp.

Serotyping and phage typing of *C. jejuni* and *C. coli*

DNA-based typing of *Campylobacter* spp.

Detection and identification of *Helicobacter* spp.

DNA-based typing of *H. pylori*

Primary isolation of *H. pylori*

Antibiotic susceptibility testing for *Helicobacter* spp. ***

* Charges are now made for this service

** Helps to ensure new or emerging pathogens or infections are identified

*** Will become an increasingly important activity, especially within the new PHLS Antibiotic Programme

Public Health:

Investigations of outbreaks of salmonellosis and Vero cytotoxin-producing *Escherichia coli* O157 infections involving international collaboration

One of the aims of the PHLS is to control the spread of infectious disease and in this respect the LEP plays a key role in relation to enteric pathogens. In early 1997 the LEP recognised a putative outbreak of *Salmonella anatum* infection in infants in England and Wales; cases of *S. anatum* infection in infants in Scotland were also identified by the Scottish Centre for Infection and Environmental Health. The ages of the cases suggested the involvement of a baby food product and a case-control study initiated by the PHLS CDSC implicated a particular brand of formula-dried milk. Through the European Union-funded international salmonella surveillance network (Salm-Net), an outbreak notification was sent electronically to collaborators in all participating countries and recent isolates of *S. anatum* from infants in France were subsequently referred to LEP for comparison with the putative UK epidemic strain. For epidemiological investigations, mol-ecular identification of the outbreak strain was urgently required and molecular analyses based on plasmid profile typing and pulsed-field gel electrophoresis (PFGE) precisely defined the strain responsible for the outbreaks in both the UK and France. As a result of these investigations the formula-dried milk product was withdrawn from the UK market and soon after from the French market. Microbiological confirmation of the involvement of the product came later, when the Food Hygiene Laboratory isolated a strain of *S. anatum* genotypically indistinguishable from the outbreak strain from an unopened packet of the product taken from the home of one of the affected infants.

Several studies in 1997 also illustrated the importance of typing in relation to epidemiological investigations of infection caused by Vero cytotoxin-producing *E. coli* O157 (O157 VTEC), not only nationally but internationally. In early 1997 two children in Finland developed haemolytic uraemic syndrome following a holiday in the Canary Islands. International communication of this information together with laboratory investigations in LEP led to the identification of a total of twelve cases linked to this outbreak. Communication was through Salm-Net (now enlarged to form Enter-net), and cases were reported in Denmark and Sweden as well as in England and Wales. Typing of all the available isolates by several methods showed that they were indistinguishable. All those affected had stayed in separate locations in a particular resort in the Canaries but were linked to a probable common source of infection by the supply of untreated water from an open well. No new cases were identified after the well had been closed.

As with other organisms in the LEP, typing of O157 VTEC involves a combination of methods in order to provide rapid and also highly discriminatory typing information. All *E. coli* O157 isolates are confirmed biochemically and serotyped. They are examined by phage typing, using a scheme that now recognises over 80

types, and for the presence of VT genes by DNA probes. Further characterisation involves VT gene subtyping by PCR and genome analysis by PFGE.

These incidents illustrate the importance of collaboration on an international basis involving epidemiologists and microbiologists in clinical, food and reference laboratories. In these examples, "outbreak" strains were identified by a combination of serotyping, phage typing and molecular fingerprinting.

Research and Development

Antibiotic resistance studies in relation to *Salmonella typhimurium* Definitive Type (DT) 104

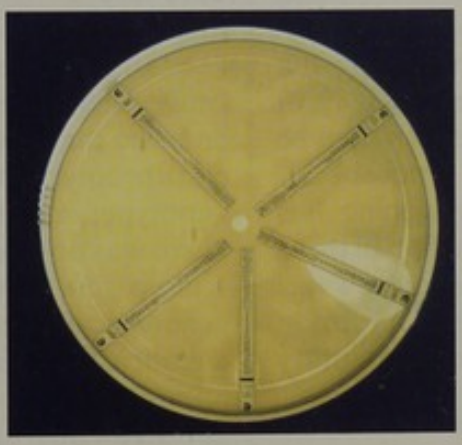
S. typhimurium DT104, a zoonotic pathogen with chromosomally-encoded resistance to ampicillin, chloramphenicol, streptomycin, sulphonamides and tetracyclines (= Resistance (R)-type ACSSuT), has become increasingly common in humans in England and Wales since 1990.

Right

Salmonella typhimurium DT104
(Antibiotic susceptibility testing by E-test)

Resistant to:
tetracyclines (TM), ampicillin (AM), sulphonamides (SU), chloramphenicol (CL)

Sensitive to:
gentamicin (GM)



Since 1994 an increase in the spectrum of resistance in *S. typhimurium* DT104 of R-type ACSSuT has been observed, with an increasing number of isolates additionally resistant to trimethoprim or ciprofloxacin, or to both these antimicrobials. Although the increase in the incidence of resistance to ciprofloxacin followed the licensing for veterinary use in 1993 of the related fluoroquinolone antibiotic enrofloxacin, the precise contribution of the use of enrofloxacin in food animals to the increase in the incidence of ciprofloxacin resistance in *S. typhimurium* DT104 remains controversial.

Chromosomally-integrated antimicrobial resistance in multiresistant *S. typhimurium* DT104 has been investigated by studying a selection of isolates for the presence of integrons using polymerase chain reaction (PCR) amplification. Integron "hot-spots" were observed in all strains conferring resistance to ACSSuT and direct DNA sequencing has identified two separated genes responsible for resistance to streptomycin and to ampicillin. It was particularly noteworthy that all isolates of *S. typhimurium* DT104 of the ACSSuT phenotype contained the same gene cassettes irrespective of source, food, animal or human, or country of origin. Resistance to ciprofloxacin was examined by amplification and sequencing of the quinolone resistance determining region in a panel of fifteen ciprofloxacin-resistant isolates. A total of four different mutations giving rise to ciprofloxacin resistance was identified.

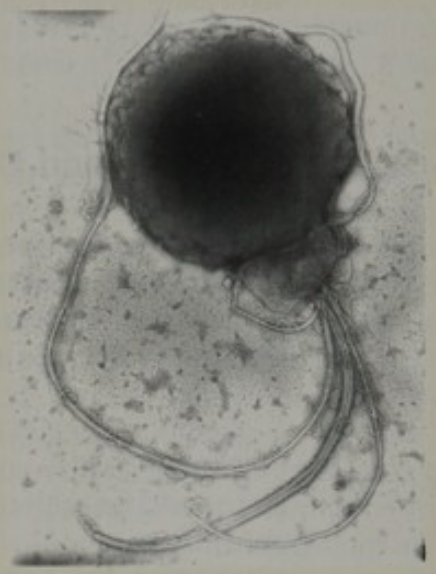
The significance of these findings is that it is now possible to compare by molecular methods both the strains and the drug resistance genes, including those responsible for resistance to ciprofloxacin, of isolates of multiresistant *S. typhimurium* DT 104 from food animals and humans. This is particularly important in relation to ciprofloxacin resistance because the identification of specific mutations in isolates from food animals can be compared with those of human origin.

Typing of *Helicobacter pylori*

Helicobacter pylori is a clinically important bacterial pathogen with major aetiological roles in peptic ulcer disease, adenocarcinoma of the stomach and gastric lymphoproliferative disorders. About 40% of the UK population is infected and an estimated 15% of these will develop dyspepsia or other symptoms. However, the major modes of transmission of *H. pylori* are not yet clear and there is also a need to study the virulence of different strains and their association with clinical symptoms. A high level of diversity exists among isolates of *H. pylori* from gastric biopsies from patients in the UK and other countries. Work by the Helicobacter Reference Unit has made significant progress in the development of genotyping. Analysis of the genes encoding urease production provides a discriminatory and reproducible fingerprinting system that groups strains from different individuals and different locations and less than 2% of isolates appear to be untypable. There is no evidence that particular urease gene profiles are linked to the occurrence of peptic ulcers.

A scheme based on the vacuolating cytotoxin genes lacks the discrimination needed for general purpose typing, but the types provide a useful way of classifying isolates, which can then be discriminated further by a novel PCR-based analysis we are developing. It is anticipated that a combination of these genotypes based on independent loci (urease and vacuolating cytotoxin genes) will provide complementary typing information.

In addition to genotyping, it is desirable to have an independent phenotypic assay, such as serotyping for rapid strain typing. O antigen serotyping of *H. pylori* requires further investigation, however, because of practical limitations of the available scheme and the recent discovery that the lipopolysaccharide of *H. pylori* has a unique structure. Lewis blood group determinants have been reported in about 80% of strains and it has been proposed that they could form the basis of a more discriminatory O antigen serotyping scheme, using four specific monoclonal antibodies.



Coccoid forms of *Helicobacter pylori* showing multiple sheathed flagella

Resistance to antimicrobial agents is an important factor in determining the outcome of *H. pylori* eradication therapy. Collaborative studies with Leeds PHL have examined the link between strain genotype and resistance and also the effect of omeprazole and clarithromycin treatment on strain genotypes at different gastric sites. There was no evidence to demonstrate a direct link between *H. pylori* strain genotype and the emergence of *in vitro* antimicrobial resistance. Most patients appeared to be colonised by a genotypically similar strain in the antrum and corpus and it appeared likely that resistance resulted from selection of variants within those populations.

Isolates of *H. pylori* from people from different parts of the world share several important conserved features, despite the high degree of genomic variation within the species. The development of relevant typing schemes is therefore feasible, particularly if schemes can be devised using an array of independent epidemiological markers. Such studies are essential for understanding the epidemiology of this organism and the identification of individuals most "at risk" from *H. pylori* infection.

Committee Membership

Dr H Chart:	Editorial Board, Journal of Applied Microbiology.
Mr T Cheasty:	Working Group for the Serotyping of Vibrionaceae, International Committee for Systematic Bacteriology.
Dr. B Rowe:	Enter-net: Project Leader WHO Expert Advisory Panel on Diarrhoeal Diseases
Dr H R Smith:	Co-chairman, WHO Working Group on Reference and Surveillance of Vero cytotoxin-producing *Escherichia coli.* Enter-net: representative for England and Wales. International Steering Committee for VTEC Symposia
Dr E J Threlfall:	Project Advisory Committee, American Water Works Research Foundation. Editorial Board, Epidemiology and Infection. Enter-net: representative for England and Wales
Mrs L R Ward:	Joint Chairman and Secretary, International Federation of Enteric Phage Typing. Enter- net: representative for England and Wales.

Awards and Distinctions

Dr B Rowe:	Order of the British Empire

Current Grants

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Development of diagnostic tests for enteroaggregative *E. coli.* PHLS Central R & D, £60,000, 1995-1998.

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The Public Health Laboratory Service case-control study of *E. coli* O157 infections in England. Department of Health, £164,715, 1996-1998.

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Food Hygiene Laboratory

Acting Director's Foreword

Dr D Roberts

The Food Hygiene Laboratory (FHL) commenced its work on 1 January 1947 and in its early years activities were concentrated mainly on the microbiological testing of milk, water and ice cream for local authorities. The work of the laboratory was later expanded into providing more extensive examination of a wide range of foods, the development of reference services (typing and toxin testing) for some of the food poisoning agents and associated research and development. A strong educational role is also adopted.

We provide a national reference facility for the microbiological examination of food, foodborne pathogens and toxins. The PHLS Food External Quality Assessment Schemes (see Yearbook section on CPHL Services) are organised by the Laboratory. We also undertake research and development in relation to all of the above activities and provide information, advice and expert opinion on all aspects of the microbiological safety of food.

Food, Water and Environmental Unit staff

During the past year a number of important developments have occurred. These include the creation of the Division of Gastrointestinal Infections, bringing together the work of the Laboratory of Enteric Pathogens and FHL with input from a strategic management group; and the decision to locate the Thames Group Food, Water and Environmental (FWE) Unit, at CPHL within FHL. This Unit serves Environmental Health Departments for the whole of London. The research and development activities are currently concentrated on toxin and toxin gene detection, including alternatives to *in vivo* testing; application of molecular methods for subtyping pathogens; and investigation and provision of reference facilities for *Cryptosporidium* and other lower eukaryotic gastrointestinal pathogens.

The Laboratory has the distinction of holding both CPA and UKAS accreditation for its activities.

Identification of *Bacillus* spp.

Serotyping of *B.cereus* and detection of toxins

Serotyping of *Clostridium perfringens* and detection of enterotoxin in faeces

Identification of *C.botulinum* and detection of neurotoxin in foods and clinical specimens

Identification of *Listeria* spp.

Subtyping of *L.monocytogenes*

Detection of *Staphylococcus aureus* enterotoxin and TSST-1

Detection of marine biotoxins (ciguatera, DSP, PSP, scombrotoxin) in foods

Detection of toxic phytohaemagglutinin in legumes

Surveillance and examination of food, beverages, water and environmental samples for the London area.

Public Health:

First Outbreak in the UK of Diarrhetic Shellfish Poisoning (DSP) associated with UK produced Mussels.

FHL staff were involved with the investigation of the first DSP outbreak associated with UK produced mussels that occurred in two London restaurants in June 1997. Forty-nine patients presented with acute (within 30 minutes) onset nausea, vomiting, diarrhoea, abdominal pain and sensation of fever for more than 8 hours. One further patient, who had probably ingested reduced toxin levels, had less severe diarrhoea. Okadaic acid (one of the algal toxins associated with DSP) was detected in mussels taken from the restaurant at levels of 25.3-36.7 µg/100g of shellfish. DSP associated toxins have previously been identified in shellfish from Europe and Japan, but North and South America, Australia, Indonesia and Japan are now affected, probably due to the increased spread of toxic dinoflagellate algae.

The only previous incident of DSP identified in the UK occurred in 1994 and developed in two people following ingestion of imported mussels.

A brief description of the 1997 incident was published in the Lancet (Scoging and Bahl. *Lancet* 1998; 352: 117).

Adult botulism associated with the consumption of home preserved mushrooms.

FHL staff also investigated an outbreak of botulism that occurred in April 1998. There were two cases (one of whom died), in members of a single family who had consumed mushrooms home-preserved in oil by a relative in Italy. *Clostridium botulinum* producing toxin type B was isolated from the faeces of both patients and from the implicated mushrooms; botulinum toxin was detected in the serum of the patient who survived, and also in the mushrooms. *(Roberts, Wales, Brett and Bradding. Lancet.* 1998; 352: 1674).

Research and Development

Cryptosporidium genotyping

A rapid method for the extraction of cryptosporidial DNA from whole faeces has been developed and applied to PCR/RFLP analysis of a number of polymorphic *Cryptosporidium parvum* genes. These techniques were applied to faecal samples collected from three waterborne outbreaks, sporadic human cases, sporadic livestock infections, and from patients infected with other gastrointestinal parasites. In two large outbreaks (Torbay 1995, N.London 1997) almost all the *C.parvum* were genotype 1: the only known host of this genotype so far identified is humans.

Isolates from a small outbreak where drinking water had been in direct contact with animals were of genotype 2. Isolates from livestock were exclusive to genotype 2, as were 35% of sporadic human infections. Both genotypes were identified in material from two patients.

Samples from patients infected with other parasites did not produce amplicons using this PCR procedure. If *C.parvum* genotype 1 is the major cause of waterborne cryptosporidiosis, the potential implications for public health and prevention of transmission through potable water are considerable.

Right

Cryptosporidium parvum meronts infecting the brush border region of enterocytes in the ileum (Electron micrograph courtesy of Dr GL Nichols, CDSC.)

FHL is offering a genotyping service for *Cryptosporidium* for a one year initial period September 1998 to September 1999.

Committee Membership

Dr D Roberts:	British Standards Institute Technical Committee AW/9 Microbiology, Meat and Meat Products, Milk and Dairy Products
	Society for Applied Microbiology, Hon Meetings Secretary
	Microbiology in Schools Advisory Committee
	Editorial Board, Journal of Applied Microbiology
	Editorial Board, International Journal of Food Microbiology
	Editorial Board, International Food Safety News
Dr J McLauchlin:	International Committee of Systematic Bacteriology: Subcommittee on the taxonomy of *Listeria, Brochothrix, Erysipelothrix* and related organisms (secretary).
Dr M M Brett:	Department of Health Infectious Intestinal Disease Executive Committee
A C Scoging:	MAFF Co-ordination of Fisheries Research and Development, Working Group on Algal Toxins
	DH/MAFF Liaison Group on Safety of Shellfish
	Corporation of London Thames Estuary Shellfish Liaison Group

Awards and Distinctions

O Mpamugo:	MSc in Food Safety Control, South Bank University. October 1997.
Dr RJ Gilbert:	Visiting Professor, Department of Farm Animal and Equine Medicine and Surgery, The Royal Veterinary College, University of London 1997-2000.

McLauchlin J.
Molecular typing of *Cryptosporidium parvum*. EU, £70,000, 1998-2001.

McLauchlin J.
Molecular characterization of *Cryptosporidium parvum*. Alcontrol, UK, £10,000, 1998.

McLauchlin J.
Prevalence of anti-cryptosporidial antibodies in sera collected as part of the PHLS Occupational Zoonoses Study. PHLS, £5,000, 1998.

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Evaluation of the use of the bioMerieux Rapid ID32A for the identification of *Clostridium botulinum*. *Lett Appl Microbiol* 1998; 8: 81-4.

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1525 outbreaks of *Clostridium perfringens* food poisoning 1970-1996. *Rev Med Microbiol* 1997; 8: Suppl 1, 64-5.

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Simple color tests based on an alanyl peptidase reaction which differentiate *Listeria monocytogenes* from other *Listeria* species. *J Clin Microbiol* 1997; 35: 2155-6.

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Microbiological criteria - collation of scientific and methodological information with a view to the assessment of microbiological risk for certain foodstuffs. *Report by the Task Group on Scientific Cooperation/Microbiology* 2.1.1997; (RJ Gilbert, Member of the Task Group).

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The PHLS Dairy Products External Quality Assessment Scheme. *PHLS Microbiol Dig* 1997; 14: 131-4.

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A survey of food safety awareness among HIV positive individuals. *AIDS Care* 1998; 10: 237-41.

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Microbiological Analysis of Food and Water. Guidelines for Quality Assurance. Amsterdam: Elsevier 1998. (D Roberts, contributor).

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Fatal *Clostridium perfringens* sepsis from a pooled platelet transfusion. *Transfusion Medicine* 1998; 8: 19-22.

McLauchlin J.
The pathogenicity of *Listeria monocytogenes:* a public health perspective. (Review). *Rev Med Microbiol* 1997; 8: 1-14.

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First outbreak of Diarrhetic Shellfish Poisoning associated with UK mussels. *Lancet* 1998; 352: 117.

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Food Microbiology External Quality Assessment Scheme 1997. Annual Report 1995-96 London: PHLS (JE Russell, D Roberts, RJ Gilbert, Organisers)

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Antimicrobial resistance in *Listeria monocytogenes* from humans and food in the UK, 1967-1996. *Clin Microbiol Infect* 1998; 4: 410-2.

Hepatitis & Retrovirus Laboratory

A WHO collaborating centre for tranfusion transmissible infections.

Director's Foreword

Dr P Mortimer

The Hepatitis and Retrovirus Laboratory (HRL) is, with the Enteric and Respiratory Virus Laboratory (ERVL), part of the Virus Reference Division. It provides reference services for the major chronic virus infections. These (human immunodeficiency virus (HIV), and hepatitis B (HBV) and hepatitis C (HCV) viruses) cause hundreds of millions of persistent infections world-wide. In England and Wales they are responsible for roughly 25,000 prevalent HIV infections, and an estimated 50,000 HBV and 100,000 HCV infections.

HRL is organised as four units. The Hepatitis and Special Projects Unit is headed by Dr Chong Gee Teo. The Retrovirus Unit and the Diagnostics Unit are both headed by Dr John Parry. (The Diagnostics Unit receives an annually renewed grant to support its joint Medical Devices Agency (MDA)/PHLS Kit Evaluation Group, led by Dr Keith Perry). The Molecular Biology Unit, which fulfils a CPHL-wide role, is headed by Dr Jonathan Clewley.

The Molecular Biology Unit provides technological support and conducts research and development in molecular genetics relevant to the work of CPHL, mostly in collaboration with other reference laboratories. HRL also distributes quality controls for the serological and molecular assays used by public health laboratories, NHS laboratories and National Blood Service laboratories.

The year 1997-98 has seen consolidation of activities in most sections of HRL, a strong publications record and some important technical advances. For instance, it is now possible to subtype both HIV and HCV, using a combination of serological and molecular approaches. The reference laboratories for hepatitis and retrovirus diagnosis are now fully integrated, and now share responsibility for all reference work on HIV, hepatitis A to G, and HTLV. This combined laboratory has been further automated and its technical staffing rationalised.

The productivity of the Kit Evaluation Group has been higher than ever this year, and the Quality Control Group (QCG) has made important contributions to diagnostic accuracy throughout the PHLS and in many NHS and other laboratories.

The Hepatitis Unit has increased its capacity to type viruses and analyse outbreaks - in February 1998 it began to investigate a large iatrogenic outbreak of HBV (see "Highlights" below). Dr Teo's externally funded collaboration with the London University Eastman Dental Institute has enabled continuing study of oral herpes viruses focusing, at present, on the Kaposi's Sarcoma-associated virus, HHV8.

The year 1997-98 has also seen a cohesive programme of work in the Molecular Biology Unit, with molecular technologies being used to increasingly good effect in virology and bacteriology. A multiplex diagnostic PCR for four respiratory viruses has been perfected in collaboration with the Respiratory Unit of ERVL. PCR has been put on a real time basis using the LightCycler instrument, and been developed with the needs of diagnostic laboratories and screening laboratories such as those of the National Blood Service in mind. To support antiviral treatment and diagnostic studies, PCR methods to quantify HIV and HCV RNAs are being developed. A similar quantitative viral DNA assay, which might replace HBeAg testing of health service staff performing exposure prone procedures, has begun to be developed in collaboration with the Hepatitis Unit.

Great strides have been made with amplified fragment length polymorphism analysis of bacterial genomes during 1998, with the resolution of several technical obstacles. Analyses of the genomes of strains of *Streptococcus pyogenes* M type 1 and of methicillin resistant strains of *Staphylococcus aureus* were completed. With the publication of the entire sequence of *Escherichia coli* Dr Arnold began to compare observed with predicted fragments of *Escherichia coli,* thereby validating the fluorescent AFLP method as a reproducible one for high resolution bacterial fingerprinting. The fluorescent AFLP development represents a new app-roach to bacterial genotyping and is expected to lead to more accurate and rapid outbreak analysis within PHLS, and a new way of typing various important pathogens.

At all levels HRL staff have worked productively and harmoniously, with an emphasis on bringing new technology to bear in reference work and research and development. The laboratory continues to enjoy substantial external financial support reflecting the confidence of sponsors outside the PHLS. Strong emphasis is placed on winning new grants to exploit technical and scientific opportunities.

The laboratory has been ably served by its administrative and secretarial staff. Close attention has been paid to consumable monitoring, instrument procurement, report turnaround times and telephone and typing services. Customer satisfaction inquiries have begun with two formal external visits, and informal contacts with other customers.

HRL looks forward to important internal and external scientific collaborations in 1998-99. The laboratory is well positioned for further development eg in investigating new hepatitis viruses, widening the scope of its applications of genomic amplification and resolving current problems e.g. in attempting to expand QC activities of QCG into the molecular fields.

Senior staff of HRL sit on several PHLS and external national committees and are becoming increasingly influential. Interactions with ERVL are close and productive at both a scientific and a practical level. Divisional unit heads and laboratory managers meet regularly on a formal basis and in numerous informal contacts. In this way the two laboratories provide a strong virological reference service to the PHLS and beyond.

Pathogen	Assay/ Investigation
Hepatitis A virus	IgG anti-HAV IgM anti-HAV
Hepatitis B virus	HBsAg HBeAg Anti HBe Anti HBc total antibody Anti HBc IgM Anti HBs IgG HBV DNA (PCR) HBV genetic differentiation studies HBV quantification
Hepatitis C virus	Anti HCV IgG HCV RNA (PCR) HCV quantification
Hepatitis D virus	Anti HDV IgG Anti HDV IgM HDV Ag
HIV 1/HIV 2	HIV antibody screen HIV antibody confirmation HIV PCR (RNA and DNA) HIV quantification HIV 1/HIV 2 differentiation HIV p24 Ag with neutralisation IgM/IgA anti HIV HIV subtyping HIV genetic differentiation studies
HTLV I/HTLV 2	HTLV antibody screen HTLV antibody confirmation HTLV PCR

Virological and bacterial outbreak investigation using molecular techniques.

Public Health:

A popular HIV diagnostic kit that gave falsely negative results

The IMx/Æ assays (Abbott Laboratories) are a popular range of viral diagnostic kits that run on a compact dedicated bench-top instrument. In early 1996 this instrument and the associated anti-HIV kit (8B32) were being used by 46 (25.4%) of 230 participants in the UK NEQAS performance assessment scheme. At the end of March 1996, however, the 8B32 kit had to be withdrawn from use in UK laboratories following reports of falsely negative results. An extensive retesting programme was undertaken, under the direction of the PHLS. A total of seven falsely negative IMx results were identified.

False negative anti-HIV results may often be due to technical or clerical error, but others are due to a specific kit defect, as was the case in this instance.

The known falsely negative reactions in IMx version 8B32, and some unexpectedly weakly positive reactions, occurred after Abbott Laboratories modified the assay in mid-1995 with the intention of improving its ability to detect infections with the rare outlier strains of HIV 1. When reports of this false negativity in the modified assay emerged, some 6 months after its introduction, the manufacturer advised customers to 'discontinue use of [the assay] or evaluate each specimen both undiluted and at a 1:4 dilution.' Abbott also suggested that the problem might be associated with 'high titre positive samples', and themselves investigated the cause of the false negative reactivity. They subsequently ascribed it to a fresh serum effect based on the presence of an intact complement system in the test sample and concomitantly high titres of antibody to HIV p24.

The Kit Evaluation Group of HRL also investigated the false negativity in the IMx/Æ HIV-1/HIV-2 3rd Generation Plus assay (8B32), and evaluated the kit that superseded it (IMx/Æ HIV-1/HIV-2 III Plus, code 8C98). Specimens were significantly more reactive in 8C98 than in 8B32 in a comparison on 574 freshly-collected anti-HIV 1 positive sera. In 8B32 the signal from 55 specimens selected because of weak reactivity was enhanced by preliminary heating at 56°C for 30 minutes. Reactivity in 8B32 was also increased in most randomly chosen anti-HIV positive serum specimens by the addition of EDTA.

Detailed investigation and evaluation showed that, the replacement kit, IMx/Æ 8C98, was the second equal most sensitive assay of ten kits examined. No evidence was found that 8C98 was prone to the effect that had given rise

to false negative results in its predecessor (8B32). The modified kit (8C98) was introduced into UK laboratories in October 1996, following this work. In March 1998 it was being used by 36 (10.1%) of 356 participants in the UK NEQAS scheme, apparently without mishap.

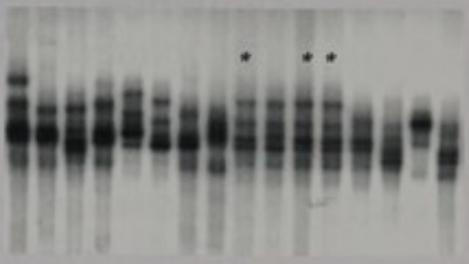
The initial survey of falsely negative IMx results was published in the BMJ in 1997 (315: 772-774) ; investigations of the mechanism of the IMx defect and the performance of the new IMx assay were published in the Journal of Medical Virology (56: 138-144) and an MDA Evaluation Report (MDA/97/57).

Hepatitis B in an alternative therapy clinic

Despite the availability of hepatitis B virus (HBV) vaccine, infections continue to occur in susceptible individuals who fall outside the UK immunisation programme. During late 1997 and early 1998 an outbreak of HBV infection occurred that was associated with an alternative therapy clinic. Colleagues in Barnet Health Authority, other health authorities and staff at the PHLS Communicable Disease Surveillance Centre became aware of cases of acute hepatitis B in people who had recently been treated by 'autohaemotherapy' in a clinic in North London.

Serum samples were initially received in HRL from seven patients with acute HBV infection, and from four clinic staff. A lookback investigation was initiated to determine the source of infection and to control the spread of the virus. Serum samples were obtained from all patients receiving autohaemotherapy from July 1997 to February 1998. Of 221 samples requested 195 have so far been received and tested.

All the samples were tested for HBsAg and for total anti-HBc antibodies. HBsAg positive samples were tested for HBeAg, anti-HBe and IgM anti-HBc antibodies.



Hepatitis B virus variation as investigated by single-strand conformation polymorphism (SSCP) analysis. Each autoradiographic band is produced from single-stranded DNA amplified from one fragment of the HBV genome. Lanes marked with * have identical banding patterns, indicating that they carry the same HBV variant. SSCP analysis is routinely used in the Hepatitis and Retrovirus Laboratory to screen clinical specimens for sequence identity in hepatitis viruses.

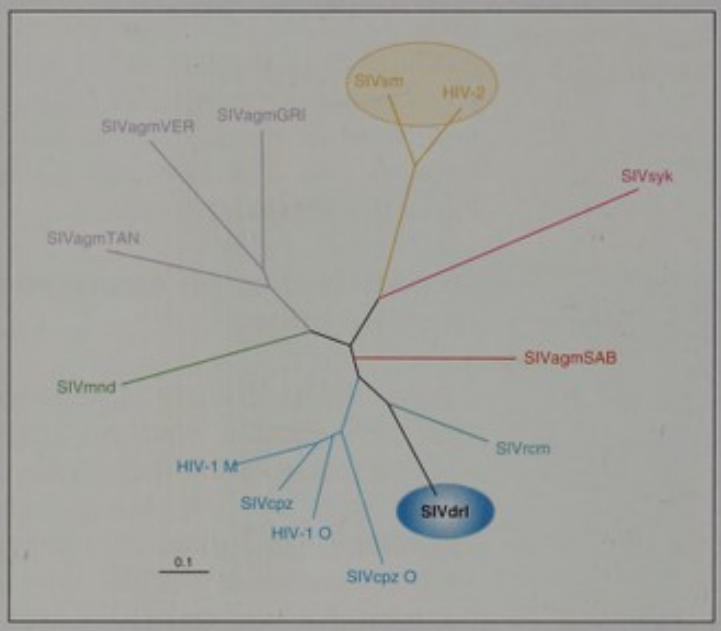
The samples were also tested for HBV DNA: regions in the HBV genome that code for the core and surface proteins were amplified by nested PCR. The PCR products were sequenced, the sequences aligned and phylogenetic trees constructed. Comparisons were made with homologous HBV DNA sequences that had been amplified during investigations of previous unrelated iatrogenic transmissions. Thirty of 32 HBV DNA positive samples contained identical surface and core gene sequences, indicating a point source. It is thought that viral contamination of a multiple-use bottle of saline was the source of the outbreak, though it remains unclear how the clinic workers became infected.

Direct sequencing of PCR products provides the highest level of discrimination when examining virus strains that might be involved in transmission events. In this lookback exercise, the comparison of HBV DNA sequences with unrelated controls and the use of phylogenetic analysis demonstrated that almost all the 32 patients were infected with the same variant of hepatitis B virus. These patients could therefore be linked to a common source of infection associated with their attendance at the alternative therapy clinic.

Research and Development

A novel simian immunodeficiency virus (SIVdrl) *pol* sequence from the drill monkey, *Mandrillus leucophaeus,* that resembles HIV 1-O.

A PCR assay was developed based on highly conserved motifs in the polymerase *(pol)* encoding gene sequences of simian and human immunodeficiency viruses (SIV and HIV). It was originally intended that this assay would be used for screening for divergent HIV strains that might be encountered in the course of investigations into aberrant serological and molecular results. Subtype A, group O HIV1 and HIV2 sequences were amplified by these primers. In addition, other novel retroviruses implicated in human disease were amplified. During the course of work aimed at clarifying the threat that simian viruses pose to humans an opportunity arose to apply the assay to DNA from the drill monkey, *Mandrillus leucophaeus.*



Figure

Phylogenetic tree showing the relationship of the SIVdrl pol nucleotide sequence to the equivalent sequence from other SIV and HIV genomes.

The SIVdrl sequence can be seen to group with the virus from the red capped mangabey, *Cercocebus torquatus*, (SIVrcm), and is also related to the human and chimpanzee viruses (HIV-1 O, HIV-1 M, SIVcpz O and SIVcpz). The other viral sequences shown on the trees are from tantalus, vervet, grivet and sabaeus African green monkeys, *Cercopithecus aethiops*, (SIVagmTAN, SIVagmGRI, SIVagmVER and SIVagmSAB); mandrills, *Mandrillus sphinx*, (SIVmnd); Sykes' monkey, *Cercopithecus mitis albogularis*, (SIVsyk); and sooty mangabeys, *Cercocebus atys*, (SIVsm). Note that human immunodeficiency virus type 2 (HIV-2) is closely related to the sooty mangabey virus (SIVsm).The scale bar indicates nucleotide substitutions per site.

The PCR assay was used to amplify pol gene sequences from uncultured drill peripheral blood mononuclear cells. DNA sequences of the amplicons obtained suggested that they were infected with a unique simian immunodeficiency virus (SIVdrl). Phylogenetic analysis showed that a 787 base-pair pol sequence was most closely related to the SIV from the red capped mangabey and to the HIV1-O group of human lentiviruses. On the basis of further PCR testing, SIVdrl is common in, but apparently not pathogenic for, drills.

Although endangered, the drill still inhabits areas of Cameroon and Nigeria with other non-human primates including chimpanzees, forest guenons, colobines, mangabeys and gorillas; exchange of SIVs between these species has therefore been possible. It is probable that there has been ample opportunity for SIVdrl to infect humans when drills are butchered for food. The HIV1 group O variant viruses have their highest prevalence in West Africa, including Cameroon and Nigeria. While further characterisation of the SIVdrl genome is required to unravel its relationships to the human lentiviruses, this work may throw light on the origin of HIV1 and may contribute to understanding the pathogenesis of the human lentiviruses. It may also be helpful in the development of a vaccine against HIV1.

Committee Membership

Dr P Mortimer	DH Advisory Committee on the Microbiological Safety of Blood and Tissues.
	DH Advisory Group on Hepatitis
	Society for General Microbiology Clinical Virology Group (Convenor)
	MDA Advisory Committee on *in vitro* Diagnostic Assays.
	National Blood Service Standing Advisory Committee on Transfusion Transmitted Infection
	Epidemiology and Infection: Editorial Board
	Emerging Infection Diseases: Editorial Board
	Journal of Medical Virology: Editorial Board
	External Examiner: MSc Virology, LSHTM
Dr J Parry	National Blood Service Advisory Group on Kit Evaluation
	WHO Temporary Adviser for HIV/AIDS
	Scientific Advisory Board, Epitope Inc. Oregon, USA
Dr J Stanley	Society for General Microbiology Systematics and Evolution Group

Awards and Distinctions

Dr C Arnold	PhD London 1997
Dr JA Connell	PhD London 1997
Dr D Linton	PhD London 1998
Ms J Newham	Diploma in Management Studies and commendation, University of Hertfordshire 1997 (awarded University prize)
Dr SL Ngui	PhD London 1998
Dr K Perry	PhD London 1996
Dr A Ridley	PhD London 1997

Current Grants

Parry JV, Mortimer PP.
Unlinked Anonymous HIV Prevalence Monitoring. Department of Health: £280K pa; 1998-2003.

Clewley JP, Parry JV.
Rapid Subtyping of HIV-1 from Serum. Department of Health: 44K pa; 1998-2000.

Parry JV, Mortimer PP.
Evaluation of Diagnostic Kits. Medical Devices Agency: £232K pa; 1997-2000.

Parry JV, Perry R, Giles R.
Evaluation of Rapid Test Devices. WHO: US $30,000; 1998-1999.

Teo CG, Harris K.
Typing of hepatitis C virus. PHLS Project Grant: £17.3K pa; 1997-2000.

Saunders N, Stanley J, Glover J.
Real time quantitative PCR for the analysis of gene expression in culture collection organisms, British Biotechnology and Science Research Council £155K pa; 1998-2001.

Stanley J, Grady R, Cookson B, (LHI).
Rapid Discriminatory Genotyping of *Staph. aureus* including MRSA and application to high throughput of strains in the reference laboratory. PHLS Project Grant: £23.3K pa; 1996-1999.

Stanley J, Lawson A, Logan J.
Prevalence of Campylobacter in human disease - a Molecular approach. Department of Health: £89,000; 1998-2000 £154K; 1996-1999.

Publications 1997/98

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Performance of the amplicor human immunodeficiency virus type 1 PCR and analysis of specimens with false-negative results. *J Clin Microbiol* 1997; 35: 2846-53.

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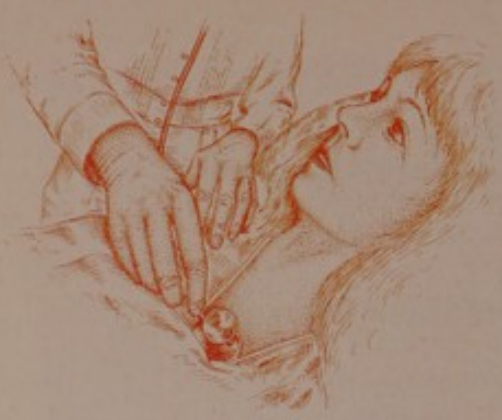


Enteric & Respiratory Virus Laboratory

A WHO Global Measles Reference Laboratory, WHO National Influenza and Polio Laboratory.

Director's Foreword

Dr D Brown

The PHLS Enteric and Respiratory Virus Laboratory is a national and international reference centre for a wide range of virus infections including Respiratory, Enteric and Zoonotic virus infections. We receive clinical samples and viral isolates from public health, National Health Service and commercial laboratories across the UK. The laboratory is made up of four units; the Respiratory Virus Unit, which is the UK National Influenza Laboratory, the Enteric Virus Unit, the Zoonotic Virus Unit, which houses a P4 Laboratory, and the Immunisation and Diagnosis Unit.

During 1997/98 a total of 24,243 reference specimens and 8,396 primary diagnostic samples were investigated in ERVL. A listing of the reference services provided by ERVL is given below. This is a similar level of testing to 1995/96 and 1996/97 and reflects the value of ERVL services to clinicians, microbiologists, consultants in communicable disease control and the PHLS Communicable Diseases Surveillance Centre.

The main focus of the laboratory's work is to provide reference services. The expertise developed through the provision of this reference service supports an applied research and development programme and we provide support for outbreak investigations in the UK and internationally, including recent involvement in WHO investigations of Enterovirus outbreaks in Cyprus and Romania and Monkeypox in Zaire. The work on this diverse range of viruses is linked by several common objectives: specifically the development of improved surveillance programmes to measure the burden and pattern of infection. This objective is underpinned by wide ranging studies of molecular epidemiology and in developing new approaches to rapid and non-invasive viral diagnosis such as the detection of salivary antibodies. The development and evaluation of the salivary diagnostic test for measles, mumps and rubella and the resultant national diagnostic service offered to primary care played an important role in demonstrating the success of the recent MR campaign.

Reference And Diagnostic Testing Services

Salivary and serological diagnosis of measles, mumps and rubella

Genotyping of measles, mumps and rubella viruses

Rubella diagnosis by PCR

Parvovirus B19 diagnosis

Polyomavirus reference (JC and BK PCR, serology)

Influenza typing (antigenic and genomic characterisation)

Influenza diagnostic serology

Influenza antiviral sensitivity

Respiratory virus multiplex PCR (including RSV A & B)

Investigation of nosocomial PIV3 outbreaks

Haemorrhagic fever virus diagnostic service

B virus reference diagnosis

HSV type specific antibody test

SRSV diagnosis and typing (PCR)

Rotavirus diagnosis and characterisation

Reference EM diagnosis

Poliovirus intratypic typing and diagnosis

Enterovirus typing

Community based surveillance and outbreak investigations

Respiratory disease

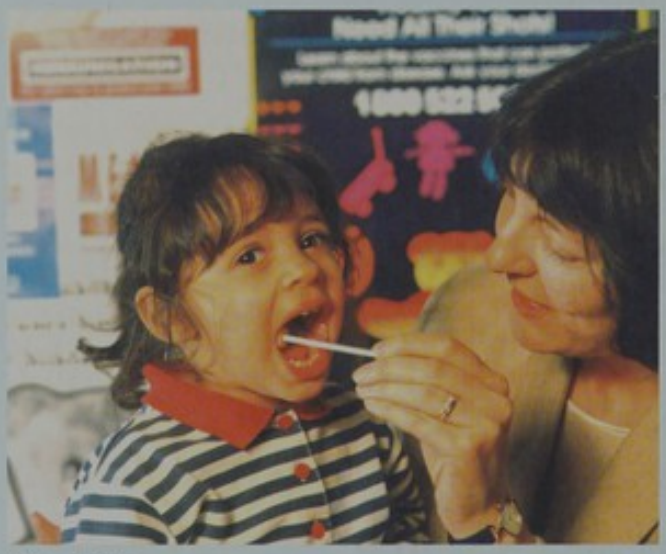
Gastroenteritis

Rash/Fever disease

Public Health: *Steiner Measles outbreak*

The measles, mumps and rubella national surveillance programme, a collaboration between ERVL and CDSC Immunisation Division, continues to investigate notifications of these vaccine preventable diseases. Around 50% of all notified infections are investigated by salivary antibody testing. Only a small percentage of clinically suspected cases are confirmed as the diseases are diagnosed clinically, providing evidence of the successful control of MMR in England and Wales.

In the summer of 1997, a measles outbreak began in a North Yorkshire village, amongst residents of a Rudolf Steiner community. Members of this close knit movement, following the philosophies of its Austrian founder, favour alternative medicine and do not accept many of the offered vaccines, believing in the physical and intellectual benefit to the child of natural infection with diseases such as measles. Consequently, most children in this village community were susceptible and the outbreak progressed rapidly. By October the outbreak had spread to a Steiner community in Gloucestershire, and thence to Bristol. In January, cases were seen in Hampshire, again within a Steiner community. The outbreak finally subsided in March 1998.



Salivary Swab

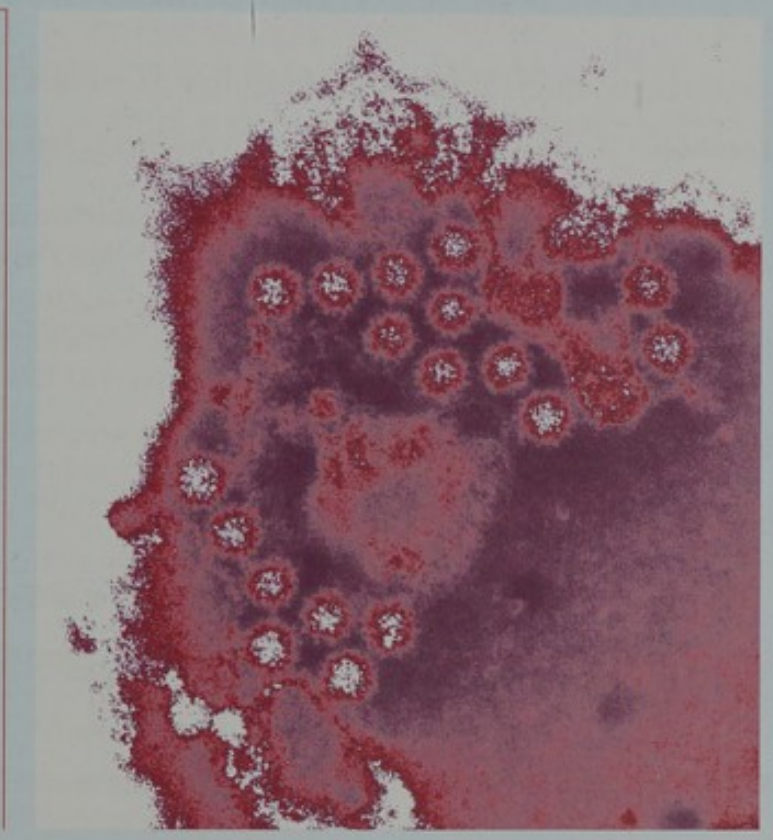
Salivary antibody testing and epidemiological data confirmed a total of 150 cases, 90% occurred in children under the age of fourteen. 146 of the cases were known to be unvaccinated. Molecular typing of measles detected from the outbreak by PCR showed the strain to be identical in all cases and closely related to a predominant measles virus strain currently circulating in Europe. No cases of measles were seen in the communities neighbouring the Steiner groups, indicating the high level of immunity in the general population. The close monitoring of this outbreak, the largest to occur in the UK since the 1994 measles/rubella booster campaign, demonstrated the value to national surveillance of the salivary testing service.

Research and Development:
New diagnostic tests for small round structured viruses

Small round structured viruses (SRSVs) cause an acute self limiting gastroenteritis and are the commonest cause of epidemic viral gastroenteritis. Outbreaks occur most frequently in nursing homes and hospitals due to person-to-person spread, where they cause a substantial morbidity. SRSVs are the commonest foodborne viral infection and their role in community acquired enteric disease is only now becoming apparent. The diagnosis of these infections is based on visualising particles in the electron microscope, which is insensitive. No widely available diagnostic reagents have been developed because the viruses cannot be cultured. In recent years several SRSVs have been sequenced and this has facilitated the development of molecular techniques to study the epidemiology of these agents.

Right

Electron micrograph of small round structured virus (SRSV). Magnification x 200,000.



In ERVL research has focused on several areas. We have developed methods to detect, quantify and characterise SRSVs in shellfish, which has enabled more detailed investigation of infection pathways in food related outbreaks. This tool will be important in developing better methods to purify the shellfish, and should contribute to reducing the burden of infection.

The SRSVs are a diverse group of viruses and we have characterised 15 distinct strains. The development of typing methods based on these strains has allowed us to investigate the patterns of infection and we have recently shown for the first time distinct epidemiological patterns of infection caused by different SRSV strains. Some SRSV strains cause periodic epidemics of disease and other strains remain endemic in the community over several years.

The use of recombinant molecular techniques has allowed virus-like particles to be produced. These have been used to develop type specific diagnostic tests suitable for epidemiological studies and work is currently underway to produce simple robust assays that can be used in diagnostic laboratories.

Committee Membership

Dr D Brown:	Department of Health, Haemorrhagic Fever Working Group
	Department of Health, Committee on UK Polio Status
	Advisor to the WHO on Rotavirus Surveillance
Dr M Zambon:	European Influenza Vaccine Strain Selection Committee
	Department of Health Joint Committee on Vaccination and Immunisation (Respiratory Virus Working Group)
	Advisor to UK Gene Therapy Advisory Group

Awards and Distinction

Dr D Brown:	Hon Senior Lecturer LSHTM
	Editorial Board. *Indian Journal of Microbiology*
Dr L Jin:	Hon Consultant, Anti-Epidemic Station of Liaoning Province, P.R.China
Dr H Appleton:	Secretary, UK Water Virology Group

Current Grants

Brown D, Green J, Cheesbrough JS, (Preston PHL), Hoffman P, (LHI).
Investigation of patterns of environmental contamination with SRSV on hospital wards and the development and evaluation of decontamination procedures. Hospital Infection Society, £40,000, 1998-2000.

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Neutralising antibodies to PIV3 in bone marrow transplantation. Leukaemia Research Foundation. £30,000, 1997-1998.

Zambon M, European Cell Culture Collection, CAMR.
Development of novel cell lines for influenza. Department of Health, £60,000, 1996-1998.

Zambon M.
Influenza surveillance. Glaxo - Wellcome, £100,000, 1997-1998.

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Investigation of Amantadine resistance of influenza A strains. PHLS Research and Development, £60,000, 1997-2000.

Zambon M, Booy R, Viner R, (Institute of Child Health).
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Development of Enzyme immunoassay for detecting SRSV. PHLS Research and Development, £160,000, 1998-2001.

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1999 Directory of Services and Specialist Functions

CPHL Services

CPHL provides a wide range of specialist services to both national and international customers. These include reference tests which are often complex or for microorganisms rarely encountered in routine diagnostic laboratories. Traditional and molecular typing methods for distinguishing individual strains of microorganisms are also available and are invaluable in epidemiological investigations.
(See List of Reference Services).

The United Kingdom National External Quality Assessment Scheme (NEQAS) for Microbiology and the PHLS Food External Quality Assessment Schemes are both operated from CPHL. These schemes have participants worldwide.

The National Collection of Type Cultures is located at CPHL. It is the largest established medical culture collection in the world offering a bacterial culture supply service.

The Media Production Department supplies the specialist culture media required for the reference Laboratories at CPHL and also manufactures media for routine diagnostic clinical microbiology and food and water microbiology for PHLS Laboratories in the South East of England.

Other services at CPHL include the PHLS Central Library, Medical Illustration and Conference facilities.

Commitment to Quality

The Central Public Health Laboratory (CPHL) is committed to a policy of providing reference services of the highest standard. The quality of the staff is seen as the main resource which contributes to maintaining the reputation of CPHL, supported by a quality system in place throughout the institute. Where appropriate, CPHL has submitted itself to third party assessment to recognised quality standards. The individual Laboratories provide widely varying services and no single accreditation standard meets all their requirements. Consequently, the quality system implemented in CPHL has to cater for the differing need of all Laboratories and Departments.

CPHL is committed to the introduction and development of an ongoing programme of quality improvement, to ensure that products and services meet or exceed the level of performance satisfaction expected by all customers. The programme is designed to lead to compliance with operational standards appropriate to the work, either BS EN ISO 9002, NAMAS, CPA or CPA EQA. As part of that programme, CPHL has an ongoing customer service strategy, in which senior staff meet customers and use the feedback to improve the quality of service provided.

All six reference Laboratories have achieved Clinical Pathology Accreditation (CPA), the Food, Water and Environmental Unit of the Food Hygiene Laboratory and performance testing of media quality control have been accredited by UKAS to the NAMAS Accreditation Standard M10. The Quality Assurance Laboratory, which organises the UK national external quality assessment (EQA) scheme for microbiology has been accredited by CPA (UK) to the EQA Standard. The National Collection of Type Cultures (NCTC) and Media Services Department have been certified by BSI QA to BS EN ISO 9002.

Specialist Functions

Reference Service list
EQA schemes
NCTC
Media
Medical Illustration
Library
Conference Facilities

CPHL REFERENCE SERVICES MARCH 1999

TELEPHONE NUMBER 0181 200 4400*

Service		Specimen required	Laboratory	Ext. no.*
Antibiotic susceptibility testing		Pure culture on agar slope	ARMRL	4237
Bacillus	– identification	Pure culture on agar slope	FHL	3521/4539
Bacillus cereus	– confirmation/serotyping	Pure culture on agar slope. Food or beverage >5ml/g	FHL	3521/4539
	– toxin/enterotoxin detection	Food or beverage >5ml/g		
Bartonella (Cat Scratch Disease)	– serology	Serum >200µl	RSIL	4331
Bartonella	– identification	Pure culture on any suitable medium	RSIL	4331
Bartonella antigen or genome detection and culture from clinical material		Whole blood, pus, skin, other biopsy material	RSIL	4331
BK and JC virus		CSF, brain biopsy, other tissues – by arrangement	ERVL	3015
Burkholderia pseudomallei	– serodiagnosis	Serum >200µl	LHI	4224/4227
Campylobacter	– identification and typing	Pure culture on charcoal swab	LEP	3772
Chlamydia antigen or genome detection and culture from clinical material		Contact laboratory	RSIL	4331
Chlamydia pneumoniae	– serology	Serum >500µl	RSIL	4331
Citrobacter	– serotyping	Pure culture on Dorset's egg or agar slope	LEP	3172
Clostridium botulinum	– isolation, identification and toxin detection	Pure culture in cooked meat medium. Food, serum, faeces, gut contents >5ml/g (smaller specimens adequate in some circumstances)	FHL	4933/4116
Clostridium perfringens	– identification, serotyping and lethal toxin detection	Pure culture in cooked meat medium	FHL	4933/4116
	– enterotoxin detection	Faeces >1g		
Clostridium tetani	– identification and toxin testing	Pure culture in cooked meat medium	FHL	4933/4116
Corynebacterium	– identification and toxin testing	Culture on blood or Loeffler agar slopes	RSIL	4536/4289
diphtheriae	– immunity and vaccination studies	Serum >200µl	RSIL	4289
Enterobacter sp.	– typing	Pure culture on agar slopes	LHI	4227
Escherichia	– serotyping	Pure culture on Dorset's egg or agar slope	LEP	3172
***Escherichia coli* 0157**	– phage typing	Pure culture on Dorset's egg or agar slope	LEP	3172
	– serology	Serum >200µl		
Gram negative identification		Pure culture on agar slopes	LHI	4233/4205
Haemorrhagic fever viruses	– serology, PCR, culture	Clotted blood	ERVL	3018
Helicobacter	– isolation	Gastric biopsy sample	LEP	3740
	– identification and typing	Pure culture on chocolate agar slope		
Hepatitis A virus	– antibody/antigen detection	Serum, saliva, faeces	HRL	3070
	– genome detection	Faeces		
	– molecular epidemiology studies			
Hepatitis B virus	– antibody/antigen detection	Serum, saliva	HRL	3070
	– genome detection	Serum		
	– molecular epidemiology studies			
Hepatitis C virus	– antibody/antigen detection	Serum	HRL	3070
	– genome detection	Serum (freshly drawn, separated from clot within 2 hours)		
	– molecular epidemiology studies	Serum		
Hepatitis D virus	– antibody/antigen detection	Serum	HRL	3070
Hepatitis E virus	– antibody/antigen detection	Serum	HRL	3070
Herpes B virus	– culture	Oral, genital, wound swabs	ERVL	3025
	– PCR/dot blot			
	– serology	Paired sera (>200µl)		
HIV 1 & 2	– antibody/antigen detection	Serum, plasma	HRL	3237
	– genome detection	EDTA treated blood		
	– molecular epidemiology studies			
HSV 1 & 2	– culture	CSF, vesicle fluid	ERVL	3225
	– PCR/dot blot			
	– type specific antibody	Paired sera (>200µl)		
HTLV I and II	– antibody/antigen detection	Serum, plasma	HRL	3237
	– genome detection	EDTA treated blood		
	– molecular epidemiology studies			
Infection control advice			LHI	4209/4274
Influenza	– culture	NPA/Throat swab	ERVL	3239
	– PCR			
	– serology	Paired sera (>200µl)		
Klebsiella sp.	– typing	Pure culture on agar slopes	LHI	4227
Lectins (toxic phytohaemagglutinins)		Beans, peas, lentils etc. >5g	FHL	3521/4113

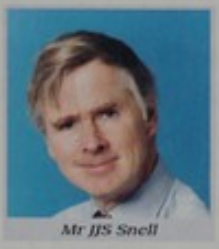
Service		Specimen required	Laboratory	Ext. no.*
Legionella	– identification and typing	Culture on BCYE or suspension in distilled water	RSIL	4331
Legionella antigen/genome detection/culture from clinical material		Respiratory samples (sputa, BAL etc.)	RSIL	4331
Legionella pneumophila – (and other Legionella) – serology		Serum >200µl	RSIL	4331
***Legionella pneumophila* serogroup 1**	– urinary antigen detection	Urine >1ml	RSIL	4331
Listeria	– identification	Pure culture on agar slope	FHL	3505/3537
Listeria monocytogenes	– serotyping and phage typing	Pure culture on agar slope	FHL	3505/3537
Marine biotoxins	– Ciguatera	Minimum 100g fish or fish products (preferably frozen)	FHL	3521/4113
	– DSP and PSP	Minimum 100g fish or fish products (preferably frozen) per test		
	– Scombrotoxin (histamine)	Minimum 10g fish or fish products (preferably frozen)		
	– Red whelk poisoning toxin	Whole animal with shell, or shell only (preferably frozen)		
Measles	– culture	T/S, urine, EDTA blood	ERVL	3203
	– PCR	Urine, EDTA blood, saliva	ERVL	3202
	– serology	Serum >200µl, saliva		
Mumps	– IGM serology	Serum >200µl, saliva	ERVL	3202
Mycoplasma	– identification	Culture on mycoplasma medium or chocolate/blood agar slope	RSIL	4331
Mycoplasma antigen/genome detection/ culture from clinical material		Respiratory samples (sputa, BAL etc.) or urinogenital samples (semen, HVS etc.)	RSIL	4331
Mycoplasma pneumoniae	– serology	Serum >200µl	RSIL	4331
Parvovirus B19	– IGM serology, dot blot/PCR	Serum >200µl, fetal tissues	ERVL	3205
Pathogenic *Escherichia coli*	– DNA probes	Pure culture on Dorset's egg or agar slope	LEP	3146
Poliovirus culture/characterisation		Viral isolate, faeces, T/S, CSF	ERVL	3018/3025
Poliovirus serology	– neutralisation	Serum >200µl	ERVL	3018/3025
Polyoma viruses	– PCR	CSF, brain biopsy, other tissues – by arrangement	ERVL	3239
	– serology	Serum >200µl		
Pseudomonas aeruginosa	– typing	Pure culture on agar slopes	LHI	4227
	– serodiagnosis	Serum >200µl	LHI	4204/4227
Respiratory virus, other	– culture	NPA/Throat swab	ERVL	3239
	– PCR			
	– serology	Paired sera (>200µl)		
Rotavirus	– PAGE Electropherotyping	Faeces	ERVL	3437/4882
	– P&G typing RT-PCR			
	–Molecular epidemiological studies			
Rubella	– serology	Serum >200µl, saliva	ERVL	3202
Salmonella (for *S. paratyphi* A & B, *S. agona, S. enteritidis, S. hadar, S. java, S. pullorum, S. thompson, S. typhi, S. typhimurium, S. virchow*)	– phage typing	Pure culture on Dorset's egg or agar slope	LEP	3132
Salmonella	– serotyping	Pure culture on Dorset's egg or agar slope	LEP	3132
Salmonella typhi	– serology (Widal)	Serum >200µl	LEP	3132
Serratia sp.	– typing	Pure culture on agar slopes	LHI	4227
Shigella	– serotyping	Pure culture on Dorset's egg or agar slope	LEP	3172
Shigella sonnei	– phage typing	Pure culture on Dorset's egg or agar slope	LEP	3172
SRSVs	– RT-PCR	Faeces (collected within 5 days of symptom onset)	ERVL	3437/4882
	– Molecular epidemiological studies			
Staphylococcus speciation		Pure culture on agar slopes	LHI	4205
Staphylococcus aureus	– phage typing	Pure culture on agar slopes	LHI	4227
	– serodiagnosis	Serum >200µl	LHI	4224
	– enterotoxin, TSST 1 detection	Pure culture on agar slope. Food or beverage >5ml/g.	FHL	4539
Streptococci (and related genera) – identification		Culture on blood or chocolate agar slopes	RSIL	4289
Streptococci	– Group A typing	Culture on blood or chocolate agar slopes	RSIL	4288
	– Group B typing	Culture on blood or chocolate agar slopes	RSIL	4289
	– Group C/G typing	Culture on blood or chocolate agar slopes	RSIL	4288
Streptococcus pneumoniae	– typing	Culture on blood or chocolate agar slopes	RSIL	4289
***Streptococcus pyogenes* serodiagnosis**		Serum >200µl	LHI	4224
Ureaplasma	– identification	Culture on mycoplasma medium or chocolate/blood agar slope	RSIL	4331
Vibrio cholerae	– serotyping	Pure culture on agar slope	LEP	3172
***Vibrio cholerae* 01**	– phage typing	Pure culture on agar slope	LEP	3172
Viral gastroenteritis	– Electron microscopy	Faeces (collected within 48 hours of symptom onset)	ERVL	3025/3437
	– RT-PCR	Vomitus, faeces (collected within 5 days of symptom onset)	ERVL	3437/4882
VTEC	– DNA probes	Pure culture on Dorset's egg or agar slope	LEP	3146
Yersinia	– serology	Serum >200µl	LEP	3172
	– serotyping	Pure culture on Dorset's egg or agar slope		

***IN CASE OF DIFFICULTY - PHONE THE APPROPRIATE LABORATORY ON THE FOLLOWING 0181 NUMBER**

LEP 358 3227 **ERVL** 358 3225 **HRL** 358 3224 **FHL** 358 3200 **LHI** 358 3299 **RSIL** 358 3101 **ARMRL** 358 3010

United Kingdom National External Quality Assessment Scheme for Microbiology

This is run by the Quality Assurance Laboratory.


Mr JJS Snell

Nature of the Scheme

External quality assessment is a process by which clinical microbiology laboratories are challenged by the introduction of samples of known but undisclosed content. Simulated clinical specimens are prepared in the organising laboratory and distributed to participants with request/report forms. Approximately 18 despatches are made each year and participants receive samples for whatever specimen types they are registered for in each despatch. Participants examine the specimens in their laboratories and report their findings to the Organiser by fax, mail or e-mail (via forms on the Internet World Wide Web (www) site). Immediately after the closing date for return of results, brief details of the intended results are posted to participants and also sent by e-mail to participants with e-mail addresses. This information is also made available on the www which allows rapid access for participants whose mail may be delayed. Reports are analysed and participants receive a summary of the overall results for the distribution and this information is also placed on the www. With the summary participants also receive a computer derived analysis of their individual results on current and recent specimens. Where 10 or more laboratories within a country participate, tables of results specific to the country are produced. Summaries and individual results analyses are normally despatched within 10 days of the closing date.

Specimens available

Specimens are currently distributed for **Bacteriology** (AAFB microscopy, General bacteriology (including antibiotic susceptibility testing), Mycobacteria culture and Syphilis serology), **Mycology** (Mycology culture), **Parasitology** (Blood parasitology, Faecal parasitology and Toxoplasma serology) and **Virology** (Anti-HBs detection, Chlamydia detection, Hepatitis B serology, Hepatitis C serology, General virus serology, HIV serology, Immunity screen (detection of IgG antibodies to HAV, CMV and VZV), Rubella IgG serology, Rubella IgM serology and Virus identification).

Subschemes for parasitology and mycology are organised jointly with the Department of Parasitology, Hospital for Tropical Diseases, London and the Mycology Reference Laboratory, PHLS, respectively. A scheme for antibiotic assays is organised from the Department of Microbiology, Southmead Hospital, Bristol.

Participants may elect to receive any combination of these specimens that they wish. The great majority of specimens are straightforward and correspond to those likely to be found in UK clinical practice. Occasionally, more challenging specimens may be distributed for educational purposes or where recognition of an unusual pathogen may be of great importance to the patient or community, eg *Corynebacterium diphtheriae* or *Vibrio cholerae*. The proportion of positive specimens is of course higher than that found in routine practice. New types of specimens are introduced into the scheme from time to time and participants are notified when these become available.

Participants

The scheme is available to both UK and overseas laboratories, 1055 laboratories participated in April, 1998 (495 UK and 560 overseas). Because of difficulties in the international postage of infectious materials, overseas participants are supplied via distributors to whom the material is sent by airfreight prior to distribution within a country. Countries where such distribution arrangements apply are currently Austria, Belgium, Denmark, Eire, Finland, Germany, Hong Kong, Israel, Italy, the Netherlands, Norway, Portugal, South Africa, Sweden and Switzerland. QAL is always interested in discussing implementation of distribution arrangements in countries not currently covered.

Future developments

Provision of EQA in gene amplification technology is seen as the priority for development and work is in progress to introduce a pilot scheme for HIV-1 RNA quantitative assay (viral load estimation) in collaboration with staff of the Hepatitis and Retrovirus Laboratory at CPHL. Other analytes will be added in due course. Development of the general serology scheme is also planned with the introduction of new analytes allowing assay by a variety of methods.

Further information:

Further details on the Schemes available can be obtained from:

Mr JJS Snell, Director, Quality Assurance Laboratory

Tel:	+44 (0) 181 905 9890
Fax:	+44 (0) 181 205 1488
e-mail:	Organiser@ukneqasmic.win-uk.net
www:	www.ibmpcug.co.uk/~ukneqasm

The PHLS Food External Quality Assessment Schemes

The Schemes

The PHLS Food External Quality Assessment Schemes have been produced and distributed by the Food Hygiene Laboratory since the first scheme was launched in September 1991. At that time there were 167 participants (UK 154, Europe and elsewhere 13) for a single scheme. At the end of the seventh distribution year total membership is 302 with 154 participants in the UK and 148 in 27 other countries; five separate schemes are currently available (see table).
The expansion in the number of schemes has been a result of requests from customers to simplify the original investigative type scheme and also to make pathogen-free samples available to those who do not undertake pathogen tests due, for example, to location of laboratories on food production sites.
Introduction of new food legislation by the EU, that required incorporation in the food law of member states, led to the development of a Shellfish Scheme, covering the requirements laid down by the EC Shellfish Hygiene Directive (91/492/EEC), and a Dairy Scheme covering the requirements of the Milk and Milk-based Products Directive (92/461/EEC). The latter Scheme is further subdivided into a pathogen and a non-pathogen option to allow participation by laboratories on dairy production sites. The most recent addition to the schemes is the inclusion of *Escherichia coli* O157 (VT negative) into the Standard and Extended Schemes.

The Samples

The samples distributed are freeze-dried microorganisms isolated from foods and at levels normally found in the real product. They cover a wide range of foodborne pathogens, indicator and spoilage microorganisms and associated background flora where necessary. Thus participants receive simulated food samples of known but undisclosed content for examination as part of their routine workload using normal staff and procedures. Results are analysed, scored and reports prepared and distributed to all customers in order that they may assess their own individual performance in relation to the total membership.

Advice and discussion

The Organisers of the Schemes offer an advisory service whereby PHLS expertise is used to help participants maintain and improve the quality of their testing. Participants experiencing problems with EQA samples are identified by analyses of scores performed after each distribution and are contacted in confidence by the Organisers. There is also opportunity for participants to meet the Organisers and each other at user group meetings; the first of such meetings was held in June 1997 and was a successful interchange of information, ideas and comment.

The future

From November 1998 there is a requirement under the provisions of the Additional Measures Food Control Directive (93/99/EEC) for official testing laboratories in EU member states to be accredited to the recognised standard (EN45000 series) and to participate in an external quality assessment scheme. Both the standard and extended PHLS Food EQA Schemes are acknowledged as appropriate for official laboratories by the United Kingdom Accreditation Service and the Department of Health and the Ministry of Agriculture, Fisheries and Food in the UK.

Flexibility

Although five basic schemes are offered to customers, the schemes can be tailored to meet the requirements of individual or groups of laboratories. For example a Scheme has been provided successfully for Italian public health laboratories, distributed by a central laboratory in Rome, for the past three years; similar arrangements are under negotiation with several other groups.

PHLS Food EQA Schemes

Scheme	Target laboratories	Frequency of distributions
Standard	European official laboratories and others offering a quality food examination service	A minimum of two samples every two months (at least 12 per annum)
Extended	Public health and other laboratories offering a wide-ranging quality food examination service	A minimum of two samples every two months (at least 12 per annum)
Shellfish	Laboratories examining raw bivalve molluscs under the current legislation	A minimum of two samples every three months (at least six per annum)
Dairy	Laboratories examining a wide range of dairy products and performing statutory tests	A minimum of two samples every six months (at least 4 per annum)
Non-pathogen	Laboratories on food production sites and those not routinely examining for pathogens	A minimum of three samples every four months (at least nine per annum).

Further information:

Details on all the Schemes can be obtained from the Organisers:

Julie Russell - Scheme Co-ordinator Ext 4119

Dr Diane Roberts - Scheme Consultant Ext 4118

Tel: +44 (0) 181 200 4400
Fax: +44 (0) 181 200 8264
e-mail: fmeqas.phls @ dial.pipex.com
droberts @ phls.co.uk

National Collection of Type Cultures

NCTC collects, preserves and supplies authentic cultures of bacteria and mycoplasmas that are pathogenic to man or other animals, that may occur in food or water and in hospital or health related environments and which can be preserved by freeze-drying. Rarely, non-pathogenic strains will be accepted where they are phylogenetically related (e.g. members of the same genus) to pathogenic strains. Bacteriophages may be accepted where they are active against pathogenic bacterial strains. Medically important plasmids are accepted only in host strains. Founded in 1920, NCTC is the longest-established collection in the world offering a bacterial culture supply service. It is internationally recognised, serving as a European Resource Centre for Plasmids and a UNESCO Microbial Resource Centre (MIRCEN). It holds and supplies some of the more popular cultures of the National Collection of Pathogenic Fungi. It provides freeze-drying services for cultures and other biologicals and is a designated International Depository Authority (IDA) under the terms of the Budapest Treaty (1977), accepting bacterial strains that can be preserved by freeze-drying and which are of medical or veterinary interest.

Further information:

For further information and/or a catalogue contact Dr Barry Holmes - 0181 200 4400 Extension 3744

Esteem Markers

Committee Membership

Dr B Holmes:	ICSB Subcommittee for the Taxonomy of *Flavobacterium* and *Cytophaga*-like bacteria (Chairman).
	ICSB Subcommittee on the Taxonomy of *Vibrionaceae,* (Chairman).
	ICSB Subcommittee on the Taxonomy of *Enterobacteriaceae.*
	Bergey's Manual Trust. Peer Reviewer, Meningitis and Special Pathogens Laboratory Section, Centers for Disease Control and Prevention, Atlanta, USA.
Dr H Shah:	ICSB Subcommittee on the Taxonomy of Gram-negative anaerobic rods, (Chairman)
	Editorial Board of : *"InScight"* (Internet service) *Clinical Infectious Diseases* Editor: *Anaerobe* *Bioscience and Microflora* Bergey's Manual Trust

Awards and Distinctions

Dr B Holmes:	1998 Bergey Award
Dr H Shah:	Visiting Professor University of East London A J Herman Fellowship from University of Western Australia Periodontal and Endodontic Society of Hong Kong Visitors Prize, 1998 Australian Society for Microbiology Visitors Award, 1998

Publications

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Citrobacter,Enterobacter, Klebsiella, Serratia and other members of the *Enterobacteriaceae*. In Balows A, Duerden BI, Eds., *Topley & Wilson's Microbiology and Microbial Infections,* 9th edition, volume 2. London: Edward Arnold, 1998; p. 999-1033.

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The Central Library of the PHLS is based within CPHL. The Library has an extensive range of books, journals, reports and reprints in medical microbiology, infectious diseases and epidemiology. Services provided include loans, photocopies, journal circulation and literature searches. Medline on CD ROM and the Library's own database are available. The PHLS Library Bulletin which includes over 350 references is published weekly; in addition an *HIV Bulletin* and a *Food and Environment* Bulletin are published monthly. They are circulated widely within the PHLS and are available on subscription outside the PHLS. The Library services are available to non-PHLS staff by arrangement.

Further information:

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The Wilson Lecture Theatre at CPHL seats 174 and has full projection and audio-visual facilities. Adjacent, there are two large well equipped seminar rooms with a video link to the lecture theatre. There are other smaller meeting rooms. Good reception desk facilities, convenient cloakroom accommodation and excellent catering facilities are available. CPHL is readily accessible by road (M1 and A1) and access to central London mainline stations is from nearby Colindale London Underground station.

Further information:

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Public Transport

British Rail
Main Line Station Hendon. Approximately 20 minutes walk from our Site. Alternatively, catch a bus, see below. From Mill Hill, take the 303 bus to our site.

Underground
Northern Line (Edgware Branch) to Colindale (Zone 4). Turn right out of the station: PHLS is a 5 minute walk down the road.

By Bus
Routes 204 and 303 pass Colindale Station. Routes 32 and 142 pass the junction of Edgware Road and Colindale Avenue.

Heathrow Airport.
Follow signs onto M4 at junction 4a and travel eastbound to junction 1. Join the A406 (north circular) here and travel north towards Hendon and signs for the M1 junction 1. From here follow detailed map on the right.

Gatwick Airport.
Follow signs onto M23 at junction 9a and travel north to join the M25 at junction 8. Travel clockwise around the M25 to junction 15 and join the M4, travel eastbound on the M4 to junction 1. Join the A406 (North Circular) here and travel north towards Hendon and signs for the M1 junction 1. From here follow detailed map on the right.

Locator Map