

**Royal College of Paediatrics
and Child Health**



**British Paediatric
Surveillance Unit**

*12th Annual Report
1997-1998*

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The Unit positively encourages recipients to copy and circulate this report to colleagues, junior staff and medical students.
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British Paediatric Surveillance Unit

A unit within the Research Division of the Royal College of Paediatrics and Child Health
50 Hallam Street

London

W1N 6DE

Telephone: 0171 307 5680

Facsimile: 0171 307 5690

E-mail: bpsu@rcpch.ac.uk

Registered Charity No. 1057744

British Paediatric Surveillance Unit - 12th Annual Report, 1997-98

Compiled and edited by Margaret Guy, Angus Nicoll and Richard Lynn, September 1998

Typeset by Philippa Davies, Royal College of Paediatrics and Child Health

Membership of Executive Committee 1997-98

Dr Christopher Verity	Chairman
Dr Angus Clarke	Co-opted
Professor Richard Cooke	Royal College of Paediatrics and Child Health Research Division
<i>to be named</i>	Faculty of Paediatrics, Royal College of Physicians, Ireland
Dr Margaret Guy	Medical adviser (<i>retired September 1998</i>)
Dr Ian Jones	Scottish Centre for Infection and Environmental Health
Dr Christopher Kelnar	Co-opted
Dr Gabrielle Lang*	Co-opted
Mr Richard Lynn	Scientific coordinator
Dr Gerald McEnery	Co-opted (<i>retired July 1998</i>)
Dr Angus Nicoll	Medical adviser
Dr John Osborne	Royal College of Paediatrics and Child Health
Professor Catherine Peckham	Institute of Child Health (London)
Dr Jon Pollock	Royal College of Paediatrics and Child Health Research Division
Professor Dan Reid	Scottish Centre for Infection and Environmental Health (<i>retired July 1997</i>)
Professor Colin Roberts	Public Health Laboratory Service
Professor Euan Ross	Royal College of Paediatrics and Child Health
Professor Brent Taylor	Co-opted
Dr Ian Lister Cheese	Department of Health (observer - <i>retired July 1998</i>)
Dr Roderick MacFaul*	Department of Health (observer)

* *from September 1998*

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Foreword

The big issue

This BPSU annual report is our "big issue". We produce other publications, but the report is the showcase for the researchers who are using the BPSU system. It demonstrates to the paediatricians who complete the cards that their efforts have a tangible and important result. We particularly hope that the report provides those paediatricians with interesting reading.

Each year the BPSU Executive Committee debates the cost of producing the annual report, because it is a significant proportion of our expenditure. The increase in size and quality inevitably results in greater cost. The committee takes the view that we should produce the best report that we can because it is important that we provide the best possible feed-back to paediatricians who are the basis of the surveillance system. In addition, the report goes to other important groups and organisations providing them with a distillation of the results of studies that have been carried out in the year. The combination of these studies is of great public health importance and this is widely recognised. The Chief Medical Officer of England and Wales, Sir Kenneth Calman, recently highlighted the work of the BPSU in his report in *Health Trends* (1997, vol 29: No3).

Financial support for the Unit is a big issue for the Executive Committee. There is major support from the Royal College of Paediatrics and Child Health - the BPSU has its home in the College. The sessions worked by the two Medical Advisers are funded by their employers - the Brent and Harrow Health Authority in the case of Dr Margaret Guy and the Public Health Laboratory Service in the case of Dr Angus Nicoll. The Scottish Centre for Infection and Environmental Health also contributes by administering the circulation of the Scottish cards. When the generous funding from Children Nationwide ceased last year there was the potential for a shortfall, although the situation was eased by an anonymous trust which gave a grant for three years. We are extremely grateful for that support. It is pleasing that an application for funds from the Research and Development Division of the Department of Health has met with a favourable response and significant funding for three years has been agreed. The application was a result of a combined effort coordinated by Dr Jon Pollock, the Principal Research Officer of our College Research Division. Our aim has always been to keep down the cost of surveillance for the individual paediatrician who wants to carry out a project - until now the full cost of having a slot on the orange surveillance card has not been borne by the individual researcher or research group. This will be an important point for discussion within the College during the next couple of years.

When we prepared the grant application for the Department of Health we were aware that the strength of our case lay in the BPSU research record - 34 completed studies since 1986, leading to over 70 publications which describe and acknowledge the work of the BPSU. However the Unit is not resting on its laurels - four new studies have already started this year and two more are approved and ready to go. The public health importance of the work can be appreciated by reading this report. Many of the studies are directly relevant to issues that have had considerable media attention in the last couple of years. For example, the study of progressive intellectual and neurological deterioration (PIND) was designed to identify any children presenting with the clinical picture of new variant CJD, a high profile subject because of the national concern about BSE. The study of haemolytic uraemic syndrome (HUS) is clearly of importance in the context of the widely publicised *E.coli* 0157 outbreaks. Two of the most recent additions to the surveillance card are of topical subjects - the study of fatal/severe allergic reactions to food ingestion and the study of subdural haematoma/effusion in under two year olds.

The BPSU team has maintained contact with other surveillance units at home and abroad. Richard Lynn, the Scientific Coordinator, has worked with the British Ophthalmological Surveillance Unit and sits on the research committee of the British Gastroenterology Research Unit. He has had discussions with the Portuguese, the Japanese and the Belgian's about the establishment of their own surveillance units. Dr Angus Nicoll, the BPSU Medical Advisor, has been to Ottawa for the second year as special advisor to the Canadian Paediatric Surveillance Programme.

We are keen to develop international contacts even further and we have proposed the establishment of an International Network of Paediatric Surveillance Units and have submitted a draft document outlining our proposals to the units that are already established in Australia, Canada, Germany, Latvia, Malaysia, the Netherlands, New Zealand, Papua New Guinea and Switzerland. All of them have responded favourably and made constructive comments. We hope to take this further, relying on the establishment of effective communication via the internet backed up by the occasional meeting, perhaps linked to an international paediatric conference.

We are very grateful to all those who have helped to maintain this high level of BPSU activity. Many thanks to all the members of the Executive Committee, which meets monthly - a considerable time commitment. We are sad to say goodbye to some members who have

worked on the committee for many years. Our thanks go to Professor Dan Reid of the Scottish Centre for Infection and Environmental Health and to Dr Gerald McEnery, Consultant Community Paediatrician. We welcome Dr Ian Jones and Dr Gabrielle Laing as their replacements. We are also very sorry to be losing Dr Ian Lister Cheese, who has been the Department of Health observer on the committee for 10 years and who has given us consistently wise advice. We will greatly miss Dr Margaret Guy who as one of the Medical Advisers has played a key role in the running of the Unit. We have already advertised for a new Medical Advisor and meanwhile Dr Angus Nicoll continues to inspire us with all the hard work that he puts into his role as the other Adviser.

Richard Lynn and his assistant Myra Schechtman have provided the central drive and support that has seen the Unit through all the changes of the past year. Without them the Unit would not function. Nor would it exist without the active support and collaboration of more than 1830 paediatricians who return the report cards. It is so important for us to maintain the enthusiasm of these collaborators in the field and we hope to improve communication with this report. We are also pleased to be able to talk via an internet web page which we will develop further both nationally and internationally. That is going to be one of our big issues in the coming year.

*Dr Christopher Verity,
Chairman, BPSU Executive Committee*

I Introduction

In July 1986 the British Paediatric Surveillance Unit (BPSU) was set up to enable paediatricians in the United Kingdom and the Republic of Ireland to participate in the surveillance and further study of uncommon disorders affecting children. The aims of the Unit are summarised in the box below.

The Unit's main concern is that of epidemiological surveillance, defined as 'the collection, analysis and dissemination of high quality data relevant to the understanding, prevention and control of medical conditions of public health importance so as to satisfy the needs of health care professionals, science, government, voluntary organisations and the public at large'. (Adapted from: Bulletin of the World Health Organisation, 1994; 72).

Several agencies collaborate in the BPSU: the Royal College of Paediatrics and Child Health (RCPCH) parent body of the Unit, the Public Health Laboratory Service (PHLS), the PHLS Communicable Disease Surveillance Centre (CDSC), the Department of Epidemiology

at the Institute of Child Health, University of London (ICH), the Scottish Centre for Infection and Environmental Health (SCIEH) which administers the scheme in Scotland and the Faculty of Paediatrics of the Royal College of Physicians of Ireland. As the BPSU monitors conditions of public health importance, an observer from the Department of Health also attends meetings of the BPSU's Executive Committee.

The Executive Committee considers individual applications and the progress of studies. Additionally, in conjunction with the collaborating agencies it formulates the Unit's longer term strategies. This has led to a five year (1996-2000) business/work plan being produced for the RCPCH which includes the challenges set out in the box below.

This report mainly focuses on activities undertaken during 1997. Reference is also made to studies and activities which have commenced in 1998.

Aims of the British Paediatric Surveillance Unit

To:

- facilitate research into uncommon childhood infections and disorders for the advancement of knowledge and to effect practical improvement in prevention, treatment and service planning
- allow paediatricians to participate in surveillance of uncommon disorders and to lessen the burden on reporting doctors of such requests arising from numerous different sources
- increase awareness within the medical profession of the less common disorders studied
- respond rapidly to public health emergencies.

June 1995 - adapted from prior documentation

Key challenges 1996-2000

The BPSU's key challenges for 1996-2000 are to:

- facilitate research and provide expert advice to members of the RCPCH and other investigators using the BPSU
- continue to disseminate information about the BPSU to the wider scientific community
- respond rapidly to challenges and public health emergencies
- ensure future funding for the BPSU
- critically evaluate and validate the reporting system
- further develop links with other national and international units involved in the surveillance of rare conditions
- educate professionals concerning the value and mechanisms of epidemiological surveillance.

February 1996 - BPSU Five year plan

2 How the surveillance system works

A study is eligible for participation in the scheme if its subject is a rare childhood disorder (or rare complication of a commoner disease) of such low incidence or prevalence as to require cases to be ascertained nationally, in order to generate sufficient numbers for the study. Though priority is given to studies of importance to public health all studies have to conform to high standards of scientific rigour and practicality. The system is open to any clinician or research group, but applicants are encouraged to approach the BPSU with, or through, a paediatrician or department of paediatrics/child health.

The number of conditions under surveillance is usually limited to 12 and there is keen competition for places on the BPSU card. Currently, the capacity of the reporting card has been increased to accommodate 14 rather than 12 conditions.

Selection of studies for inclusion in the scheme

The BPSU application procedure consists of two phases: in phase one, a short study protocol is requested covering no more than two sides of A4 paper. This should include the background to the proposed study, a case definition, likely number of reports per month, the questions which the study aims to answer and details of financial and academic support. At this stage the Scientific Coordinator and Medical Advisers offer guidance on the application before it is submitted to the BPSU Executive Committee. The committee which meets every 4-6 weeks is comprised of consultant paediatricians (general and specialist), epidemiologists and specialists in public health.

At the phase one stage, for a number of reasons many studies are found to be unsuitable, or rather that the BPSU is not suitable for answering the study's protocol. The condition may be too common and therefore may place too great a burden on paediatricians for reporting or follow-up; there may be no suitable case definition; the aim of the study may constitute audit rather than surveillance ~~and research~~; or data may be obtainable more easily elsewhere. In addition some studies present insuperable practical difficulties. If a study is not accepted, the committee always tries to advise the applicant on alternative means of undertaking the work. Once the committee agrees that the protocol is suitable, a phase two application is requested. This should provide full details of the methodology and aims of the study along with the practicalities of how the study is to be administered. Factors which increase the likelihood of a study being accepted are listed in the box. The BPSU will always help potential investigators, especially those with less experience in research methods, to develop potentially valuable studies.

Though considered stringent, the advantages of this procedure are two-fold. Firstly, respondents know that a study must be methodologically sound for it to appear on the orange card, and are thus more likely to contribute data. Secondly, whilst prospective investigators know that if their study is placed on the card they are assured of a high level of involvement from clinicians.

Finally, all studies must have evidence of receiving ethical approval. Though this is the responsibility of the investigators the BPSU urges that there is compliance with the Caldecot Report (Report on the Review of Patient-Identifiable Information, NHSE, December 1997) on data confidentiality and information flow.

Factors that favour acceptance by the British Paediatric Surveillance Unit

- scientific importance.
- rarity of the condition, though short term or geographically limited studies of commoner disorders are considered.
- proposals with outcomes of clear importance to public health.
- uniqueness, priority will not be given if similar studies have recently been undertaken or if other data sources are readily available (although the BPSU encourages the use of alternative data sources for validation and completeness of reporting).
- attention to detail, in terms of clear achievable objectives, practicability, patient confidentiality and resources.
- practicality and limited workload placed on the reporting paediatricians.
- ethical approval.

The reporting system

Participants in the reporting system include consultant paediatricians who are either members of the RCPCH or the Faculty of Paediatrics of the Royal College of Physicians of Ireland. Mailing lists are regularly updated by the BPSU office by monitoring new consultant appointments, retirements etc.

In recent years, consultants working in a number of other specialties have also been invited to participate in the scheme to help ascertain cases of conditions which are also seen by them. For example, since 1992 pathologists who are not members of the RCPCH have also

been included in the reporting scheme. In addition, most studies of infections use laboratory reports to microbiologists. Current studies that are benefiting from such multiple ascertainment include HIV/AIDS, congenital rubella, Reye syndrome, *haemophilus influenzae* infection and most recently subdural haematoma.

Surveillance is 'active' in that the stimulus to report, the orange card, comes from the Unit (Figure 1 overleaf). Each month, all those participating in the scheme are sent an orange card listing the conditions currently under surveillance. A set of instructions for completing the card, including case definitions of the conditions listed on the card is also circulated. When a new study begins, the mailing also includes a specially produced study protocol card and other information about the study.

Respondents are asked to return the card to the BPSU office, indicating the number of cases of each condition on the card which they have seen during the preceeding calendar month. Scottish paediatricians return their completed cards via the Scottish Centre for Infection and Environmental Health. When reporting a positive case respondents should complete and keep the tear off section of the card.

Participants are expected to return cards even if they have no cases to report - there is a "nothing to report" box on the card for them to tick. This is an important feature of the surveillance scheme as it allows non-responders to be identified and followed-up - reminders are sent to all participants in the scheme who have not returned their card for two consecutive months. Overall compliance rates are continually monitored.

Follow-up and confirmation of case reports

When cases are reported, the BPSU informs the relevant research team who contact the reporting clinician for further information about the case, in accordance with the agreed protocol for the particular study. Particular care is taken to ensure that questionnaires sent to reporting doctors are as short as possible, clear, straightforward and not excessive in their demands. The researchers subsequently report back to the BPSU on the outcome of each case follow-up, indicating when they have been confirmed as meeting the case definition and identifying duplicate case reports - this is particularly likely to occur when the condition requires referral to a tertiary unit.

This completeness of reporting is known as the 'completion rate'. Table 1 (page 10) shows the number of cases reported to the BPSU from its inception until the end of 1997 for all the conditions under surveillance during 1997. The number of cases which have so far been subsequently confirmed as meeting the case definition are also shown.

The time taken to follow-up a case report varies greatly between conditions and may be longer if microbiological or pathological details are required to confirm a case. The rate of follow-up is high. For example, by the end of June 1998, of the conditions under surveillance at the end of 1997, 331 (9%) of the 3746 case reports had yet to be followed-up. The final proportion of case reports which are successfully followed-up averages between 95 and 100%, though the Unit is aware that studies requesting specimens may have a lower ascertainment rate.

Table 2 (page 10) summarises the outcome of the follow-up of all cases reported to the BPSU by the end of 1997 and provides evidence for the high level of accuracy of reporting by participating clinicians. By the end of June 1997, 968 (28%) of the 3746 cases reported had been classified as reporting errors - details of the system used to classify case reports are set out in the box below.

Classification of case reports

Valid reports:

Cases confirmed at follow-up as being both unique (ie. not a duplicate) and satisfying the diagnostic criteria set out in the case definition. Confirmed cases reported to the BPSU but already known to the research worker from another source are included.

Invalid reports:

These include:

- duplicate reports of cases already reported to the BPSU, and
- reporting errors arising as a result of a misdiagnosis, the wrong box on the orange card being ticked, the case not meeting the diagnostic criteria set out in the case definition or an inability to follow-up a case.

Outcome not yet known:

Outcome of follow-up not yet received by BPSU (by June 1998).

Difficulties in case reporting

Though the BPSU has many strengths its Executive Committee is aware that reporting is never complete, and like any reporting or surveillance system some under-reporting always occurs, reasons for which are listed in the box overleaf. The likelihood of under-reporting can usually be reduced by careful design and scrupulous attention to detail during the running of the study.

However, it always has to be borne in mind that complete reporting is rarely achievable and it is not always necessary and excessive 'hounding' of reporters can be counter productive.

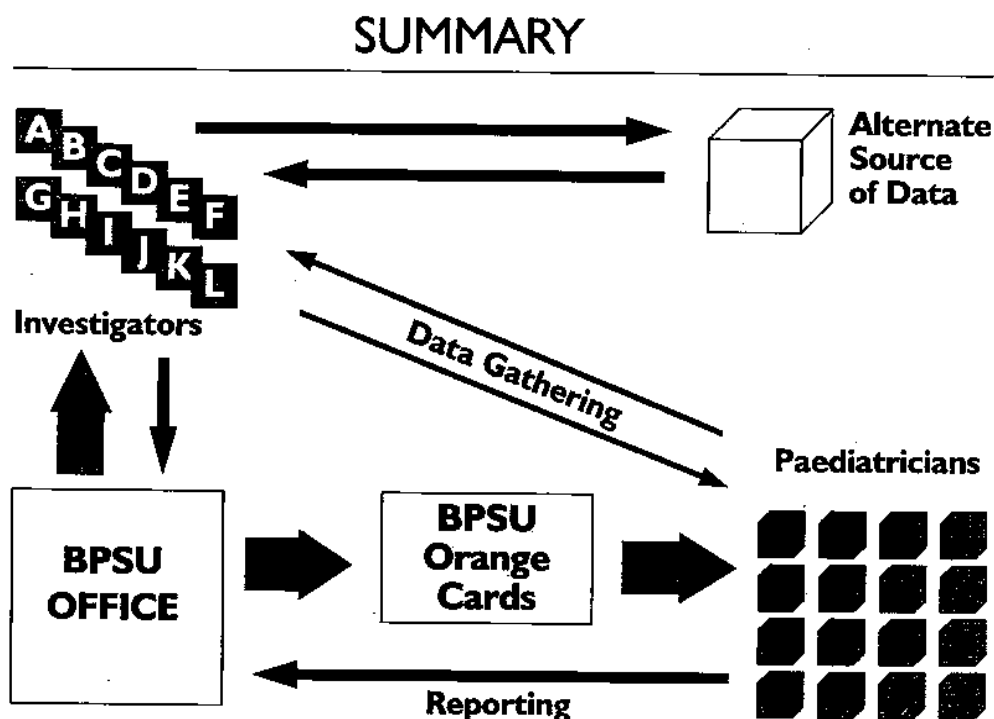
Reasons for incomplete case reporting

- Cases not seen by paediatricians
- Condition is hard to define
- Condition not easily recognisable
- Condition diagnosed but not reported

As highlighted some conditions under study may have necessarily complex case definitions, these can be off putting to reporters and lead

to underascertainment. Some researchers are coming up with a solution to this problem by devising two kinds of case definition. Firstly, a surveillance definition, concise and simple to use, sensitive but relatively non-specific (ie. producing quite a few false positives) and secondly an analytic case definition which the researcher applied to the cases reported. This second definition can be as complex as the researcher requires, though the reporter is aware of this definition through the protocol card, they are not expected to use it in reporting. Paediatricians, however, often find these complex analytic definitions useful in diagnosing cases of very rare conditions.

Figure 1



The use of complementary data sources

A distinctive and powerful feature of the BPSU system is the ability to use data from complimentary sources to validate the surveillance system, to increase case ascertainment and to increase the accuracy of data (Figure 2). The first complimentary data source to be used were laboratory reports to the PHLS of infectious disease. In the past year the *Haemophilus influenza*, HIV/AIDS, congenital syphilis and SSPE studies have included this additional ascertainment. Other sources which have been used include death registration (Reye syndrome), hospital episode data (insulin dependent diabetes, congenital dislocation of the hip) and birth registrations (higher order births). In order to increase ascertainment of congenital cataracts paediatric ophthalmologists were involved in surveillance. The use of multiple sources of data has shown to improve case ascertainment, the completeness of which varies between studies and conditions, according to the ease of case ascertainment and the availability of complementary data sources.

The Unit uses a number of 'rates' in assessing the BPSU performance and that of an individual study, and these are highlighted in the box below.

BPSU assessment rates

Reporting rate	Percentage of orange cards returned each month.
Report completion rate	The proportion of cases reported to researchers where an outcome has been reached, i.e valid, invalid etc.
Ascertainment rate	A more abstract rate indicating the proportion of all true cases (meeting the surveillance case definition) that are estimated to have been reported.

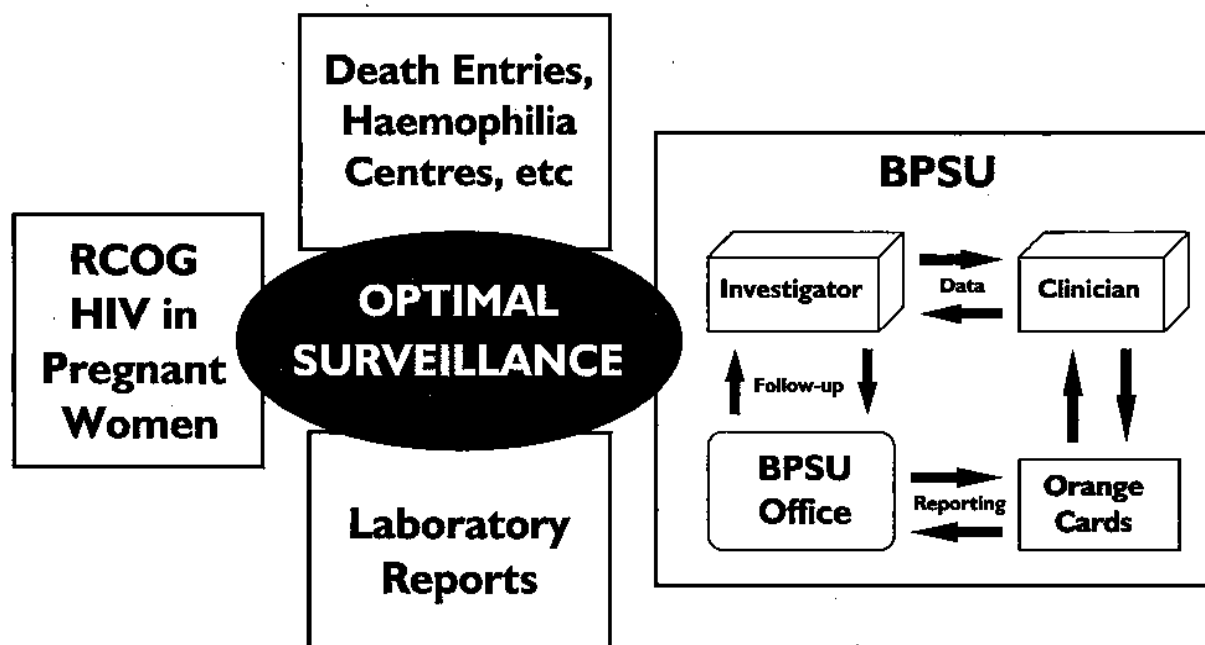
Funding

The BPSU asks research teams to contribute a sum to cover the printing and distribution of the orange cards, and where possible the other administrative and costs of coordinating the study. In 1997 the minimum sum was £210 per month.

The remainder of the Unit's costs in 1997 were met through an anonymous donor. Further non-cost support is received from the Royal College of Paediatrics and Child Health, the Public Health Laboratory Service, Brent and Harrow Health Authority and the Scottish Centre for Infection and Environmental Health.

Figure 2

Surveillance - The Bigger Picture HIV/AIDS in the UK



3 Surveillance activities in 1997

Nineteen ninety-seven saw the beginning of three major surveys each of public health importance. Following increased concern over the number of reported cases of *E.coli* 0157 infections a second survey of haemolytic uraemic syndrome started in February, (the first survey by the BPSU was in 1988); this was followed by surveillance of hepatitis C virus (HCV) infection as part of the government's £2m initiative to investigate the epidemiology of HCV in the UK. The third survey to commence was initiated from within the BPSU committee. With the support of the Department of Health, surveillance for progressive and intellectual neurological deterioration commenced in April in order to answer the question of whether there is any new variant CJD in UK children.

A further fifteen study applications were received, 12 of which are actively being considered. Already in 1998 four new studies have commenced resulting in 14 studies currently on the orange card. During 1997 two studies ended, pyridoxine dependent seizures and neonatal meningitis. Thirty-four studies have now been completed since the BPSU began in June 1986 - those completed prior to 1997 are listed in Appendix A. Researchers are encouraged to inform the Unit when data gained through the BPSU is published or presented. Known publications and presentations in 1997/98 relating to these studies and the Unit's work, totalled 26 are listed in Appendices B and C.

Other activities within the Unit include advising other medical societies in the development of their own surveillance systems, and preparations to place the BPSU on the internet. The Unit continues to liaise with the other national paediatric surveillance units. It is hoped that this will develop further through the establishment of an international network of paediatric surveillance units. The international scene is described more fully in Chapter 7.

Participation in the scheme during 1997

The BPSU ascertains the names of new consultants primarily through the RCPCH membership office, BMJ adverts or through personal communication. The number of consultant paediatricians participating in the scheme during 1997 rose to 1830, an increase of over 10% compared with the previous year. The increase is partially due to the continued expansion in consultant numbers but also due to the BPSU's increased ability to identify such new posts swiftly. Thanks particularly go to the regional advisers who took time to check the BPSU listings, supplying amendments for their areas where necessary. It should, however, be noted that some

paediatricians who hold consultant status are excluded as they do not undertake relevant clinical work, or else colleagues report on their behalf. The BPSU mailing list also includes selected groups of consultants other than paediatricians i.e. cardiologists, clinical geneticists and pathologists. In order to help in the ascertainment of cases of subdural haematoma this past year has also seen the inclusion of forensic pathologists, and our thanks are extended to the Royal College of Pathologists for supporting this initiative.

Compliance rates for returning the orange cards remains high, - the overall response rate for 1997, calculated as a proportion of orange cards returned, was 93.4%, slightly down on 1996 (94.0%). Monthly response rates ranged from 90.7% in November 1997 to 95.8% in January 1997, with a median of 93.2%. Respondents who appear not to have returned cards for two consecutive months are sent letters, as much to verify postal address as to act as a reminder. Of those responders not returning cards less than 1% are persistent.

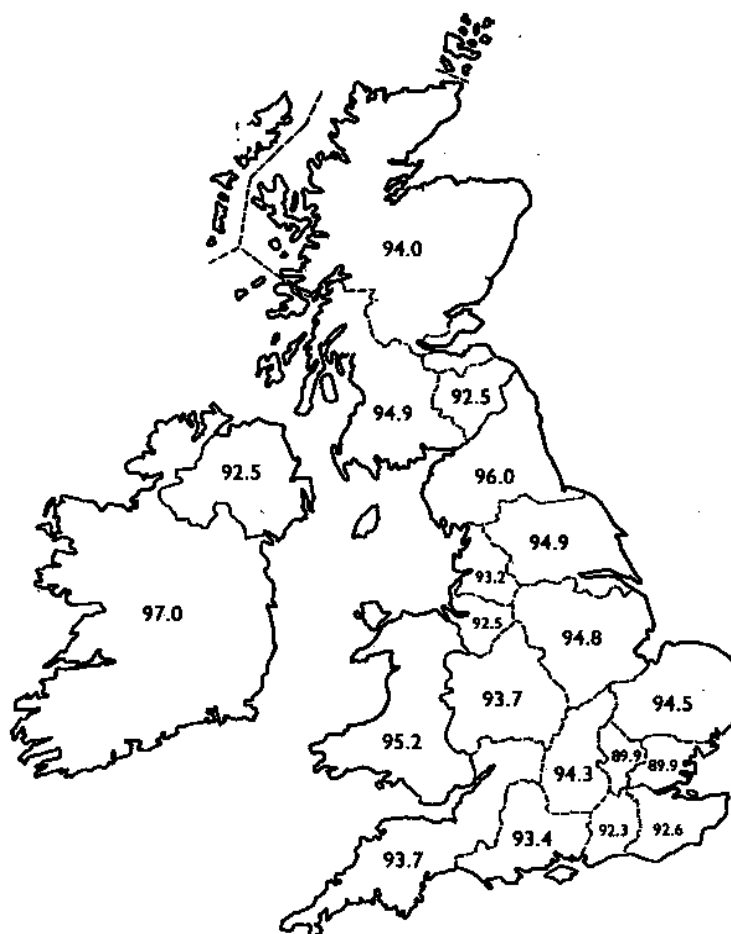
As in previous years, reporting rates varied considerably across the country, as is shown in Figure 3. Paediatricians in the Republic of Ireland achieved the highest average yearly response rate - 97.0%. Compliance was lowest in North East Thames and North West Thames at 89.9%. With regard to rank order, West Scotland and Trent regions rose by 11 and 9 places respectively, whilst Northern Ireland and Mersey fell by 12 and 11 places respectively. Once again, collectively, the Thames regions were the poorest responders with three of the four regions taking the three lowest ranking positions. The effects of regional reporting variations on case ascertainment is currently being examined by the Unit.

It is also interesting to note that a recent anonymous survey of respondents by the Australian Paediatric Surveillance Unit showed that 5% of their respondents admitted returning cards with 'nothing to report' despite knowing of a case (some assuming others would notify) and 1% failed to return a card despite knowing of a case (personal communication).

Workload of those participating in the scheme

The BPSU continually monitors the workload of participants in the scheme in terms of the number of cases reported. 54% (1225) of participants reported no cases in 1997, 44% (802) reported between one and four cases and only 2% (45) reported five or more cases. The greatest number of cases reported by a single paediatrician was 49. The orange card in 1997 carried a number of disorders affecting neonates thus neonatologists were proportionally burdened with having to report cases i.e. neonatal meningitis, congenital cataract, HCV, congenital syphilis and rubella.

Figure 3 Average orange card return rate (%)
by area, 1997



Overall average orange card return rate = 93.4%

Table 1 Cases reported from June 1986 - December 1997 of conditions under surveillance during 1997
(cases confirmed by July 1998 shown in brackets)

Condition under surveillance	Date when reporting began	Reports (confirmed cases)					
		June 1986 to Jan 1990 to		Jan 1993 to		1996	1997
		Dec 1989	Dec 1992	Dec 1995			
HIV/AIDS	June 1986	137 (90)	495 (386)	359 (214)		157 (104)	157 (82)
Reye's syndrome	June 1986	149 (76)	71 (31)	57 (18)		13 (9)	9 (7)
SSPE	June 1986	84 (50)	55 (29)	28 (14)		6 (2)	11 (2)
Congenital rubella	Jan 1991	-	43 (27)	29 (12)		23 (13)	10 (2)
Hi infection	Sept 1992	-	25 (20)	146 (106)		72 (48)	64 (43)
Pyridoxine dependency	Sept 1995	-	-	15 (8)		26 (9)	8 (3)
DKA	Oct 1995	-	-	24 (5)		24 (9)	39 (13)
Neonatal meningitis	July 1996	-	-	-		160 (103)	304 (214)
HCV	Feb 1997	-	-	-		-	451 (354)
HUS	March 1997	-	-	-		-	176 (57)
PIND	April 1997	-	-	-		-	319 (207)
Total		370 (216)	689 (493)	658 (377)		481 (297)	1548 (985)

Tables exclude previously completed studies (see page 38).

AIDS/HIV	Acquired immune deficiency syndrome/human immunodeficiency virus: reports of AIDS in June 1986 included all cases previously seen; case definition extended to include HIV infection in January 1990.
SSPE	Subacute sclerosing panencephalitis: a) reports of SSPE in June 1986 included all cases seen in the previous 12 months; b) cases 'not confirmed' include those outside England and Wales which are not followed-up by CDSC.
Hi infection	Invasive <i>Haemophilus influenzae</i> infection, pre Oct 1995 Hib vaccine failures only.
DKA	Cerebral oedema following diabetic ketoacidosis.
HCV	Hepatitis C infection.
HUS	Haemolytic uraemic syndrome.
PIND	Progressive and intellectual neurological deterioration

Table 2 Outcome of follow-up of the cases reported up to December 1997 of conditions under surveillance during 1997

Condition under surveillance	Valid reports (%)		Invalid reports			Not yet known (%)		Total reports
			Duplicates	Errors	(Total %)			
HIV and AIDS	876	(67)	183	219	(31)	27	(2)	1305
Reye's syndrome	142	(47)	41	105	(49)	11	(4)	299
SSPE	97	(53)	28	30	(32)	29	(15)	184
Congenital rubella	54	(51)	23	26	(47)	2	(2)	105
Hi infection*	217	(71)	16	67	(27)	7	(2)	307
Pyridoxine dependency	20	(41)	4	23	(55)	2	(4)	49
DKA	27	(31)	16	36	(60)	8	(9)	87
Neonatal meningitis	317	(68)	56	65	(26)	26	(6)	464
HCV	354	(78)	30	29	(13)	38	(8)	451
HUS*	57	(32)	3	0	(2)	116	(66)	176
PIND	207	(65)	18	37	(17)	57	(18)	319
All	2368	(63)	418	637	(28)	323	(9)	3746

* Studies in which validation depends on microbiological/pathological details.

4 Main findings of studies undertaken in 1997

A study has been undertaken on **cerebral oedema/death associated with ketoacidosis in diabetic children**. The findings of this study have emphasised how important this condition is, in that of 20 children who developed cerebral oedema, five died from their condition, a 25% mortality rate. The data are now being analysed to look for factors that might have predicted the severity of the condition and avoided these tragedies.

The survey of **congenital rubella** demonstrated the general success of the UK's programme of immunising young children against rubella within the MMR vaccine programme. However, it also shows that the potential for return of rubella remains in that in 1996 there were 12 cases of congenital rubella coinciding with a small outbreak of rubella predominantly among young men. It is hoped that as the cohort of immunised children work their way through to older age groups, this phenomenon can be avoided.

A new survey for the BPSU in 1997 was **haemolytic uraemic syndrome (HUS)**. In the UK this is usually caused by infection with *E.coli* 0157 an 'emerging infection' and HUS surveillance takes place in parallel with laboratory reporting of *E.coli* 0157. 0157 is well known to the public because of the Lanarkshire outbreak. The paediatric HUS and laboratory reporting demonstrate the number of children suffering damage to their kidneys from *E.coli* which is now the largest single cause of paediatric renal failure. A particular hazard identified were children visiting 'open farms', unless safety precautions were adhered to contamination can occur through food, water and unpasteurised milk.

The survey of **hepatitis C infection (HCV) in children** has demonstrated that most infections are now probably historic and mother to child transmission is fortunately much rarer than for HIV. The children in this study will now be followed-up to answer currently unknown questions about their natural history of HCV infection.

The survey for **paediatric HIV infection and AIDS** has formed the bedrock of surveillance for this infection in children since the mid 1980s. This year's data highlight the rising number of children acquiring HIV from their mother's infection. They also demonstrate the tragic situation that the number of such infections could be drastically reduced simply by applying known methods that minimise the risk of mother to child transmission. It was particularly noticeable from AIDS reports that many mothers only become aware that they are HIV infected when their child developed AIDS. They then had to cope with not only the awareness of their own and their child's infection, but often that of their male partner and the knowledge that their child's infection might have been prevented. To overcome this situation data from the survey contributed to the national intercollegiate report on reducing mother to child HIV transmission.

Surveillance for **invasive *Haemophilus influenzae* infection** has highlighted the high efficacy of vaccination against this infection which began in 1993. A surprising finding has been that levels of asymptomatic *Haemophilus influenzae* infection has declined as well as invasive disease. The study has also shown that the UK's economical strategy of only giving three primary immunisation courses to infants without later boosters seems to have no disadvantage compared to countries that use four or more injections. The study this year has also shown that there will be no particular benefit to having a different immunisation schedule for premature babies.

A second national survey of **neonatal meningitis** finished in 1997 and demonstrated that the incidence of this often fatal condition has changed little since an earlier survey carried out between 1985 and 1987. It also demonstrated again the importance of group B streptococcal infection which accounted for nearly half the infections.

Surveillance of **pyridoxine dependent seizures** has confirmed that these are very rare, but that the condition probably remains under-diagnosed and therefore under-treated as this was the only explanation for some peculiar geographical variations in the incidence of the condition.

A new survey starting in 1997 was that of **progressive intellectual and neurological deterioration (PIND) in children**. This directly government supported survey was set-up as an "emergency" study to look for any new variant CJD in children. It has been going for just over a year and fortunately, so far, it has found no cases of new variant among the very many children who present to paediatricians with chronic and worsening neurological conditions.

In contrast to the PIND study, surveillance for **Reye syndrome** is one of the oldest of the BPSU surveys having been going since 1981 which makes it older than the Unit itself. There are only seven reports received in 1996/7 the lowest total ever, none of which were associated with aspirin which has been demonstrated to cause Reye syndrome. Two of the children turned out to have unrecognised metabolic disorders demonstrating the importance of investigating fully all children presenting with Reye. The investigators also note the international importance of Reye as the first case of 'chicken flu' (H5N2 strain) in Hong Kong in 1997 was a child developing Reye following influenza and being given aspirin.

BPSU surveys often have negative findings which are as important as positive results. That is true for the surveys of invasive *Haemophilus influenzae*, congenital rubella and also in the case of surveillance for **SSPE** which found six cases in the last year, two of which were in Asian children confirming the increased risk of measles amongst immigrants who are more likely to have missed out on immunisation. The important negative finding was that there was no increase in SSPE associated with the mass vaccination campaign of MR (measles rubella) of 1994.

5 Surveillance studies undertaken in 1997

Conditions included in the scheme during 1997

During 1997, eleven conditions were the subject of surveillance. Two studies, pyridoxine dependent seizures and neonatal meningitis were completed and three studies commenced, haemolytic uraemic

syndrome, hepatitis C infection and progressive intellectual and neurological deterioration. The studies are listed in Table 3 below. Studies commenced in 1998 are described in Chapter 6.

Table 3 Studies underway in 1997

Page	Study	Principal researchers	Research institutions
12	Cerebral oedema following DKA*	J Edge, D Dunger	John Radcliffe Hospital
13	Congenital rubella*	P Tookey, C Peckham	ICH (London)
14	Haemolytic uraemic syndrome*	M Taylor, B Adak, B Rowe, S Locking	B'ham Children's Hospital, PHLS, SCIEH
16	Hepatitis C infection*	D Gibb, P Neave, P Tookey	ICH (London), SCIEH
18	HIV/AIDS infection in childhood*	P Tookey, A Nicoll, D Goldberg	ICH (London), PHLS, SCIEH
20	<i>Haemophilus influenzae</i> infection*	P Heath, M Slack, R Moxon, N Begg	PHLS, National Haemophilus, Ref. Lab. Oxford
22	Neonatal meningitis	S Halket, D Holt	Queen Charlotte's & Chelsea Hospital
23	Pyridoxine dependency	P Baxter	Sheffield Children's Hospital
24	Progressive & intellectual neurological deterioration*	C Verity, G Devereux, A Nicoll, R Will	Addenbrookes, PHLS, National CJD/SU
25	Reye syndrome*	S Hall, R Lynn	Sheffield Children's Hospital/BPSU
28	Subacute sclerosing panencephalitis*	E Miller, N Begg	PHLS

* Studies still in progress to September 1998

Cerebral oedema and death following diabetic ketoacidosis

Background

Cerebral oedema is a devastating complication of diabetic ketoacidosis (DKA) in children, and appears to be sporadic and unpredictable. The most recent figures available show that between 10 and 15 children under 20 years of age die each year from DKA in Britain, and that 80% of the deaths in children under 12 are due to cerebral oedema.

The incidence of non-fatal cerebral oedema in Britain is not known, neither is the aetiology understood. Even with optimum management by current standards, cases still occur. Retrospective studies suggest that cerebral oedema is more common in children with newly diagnosed diabetes, especially in children under five years of age. Possible contributory factors include the severity of DKA, the rate and/or quantity of intravenous fluid administration, a fall in plasma sodium concentration and hypoxia following bicarbonate administration. Animal studies have suggested that insulin itself is required for cerebral oedema to occur. There have been no sizeable case-control studies to support any of these theories.

This study aims to compare the clinical course of cases of cerebral oedema with controls with DKA but without cerebral oedema, ascertained by a separate reporting mechanism which has been developed by the investigators. This will be the first large prospective case-control study in this important area of research.

Objectives

- 1 To analyse all deaths attributable to DKA and all cases of cerebral oedema (whether fatal or not).
- 2 To establish an independent national procedure for the ascertainment of cases DKA in the childhood population.
- 3 To estimate the absolute risk of cerebral oedema among children with diabetic ketoacidosis.
- 4 To identify factors in the clinical presentation and subsequent clinical course of the child with DKA which may influence the development of cerebral oedema.
- 5 To study the outcome of cerebral oedema in Britain in terms of mortality and morbidity.

Case definition

- 1 Sudden or unexpected deterioration in conscious level in a child with diabetic ketoacidosis.
- 2 Any death during assessment or management of DKA.

Study duration

October 1995 - September 1998.

Results

From October 1995 until February 1998, 88 returns were made to the BPSU. To date, questionnaires have been returned on 75. Six were retrospective cases, occurring before October 1995, 12 were reporting errors or non-cases and 18 were duplicate reports. Of the remaining 39 cases, there were four deaths during ketoacidosis which were not due to cerebral oedema. There have been 20 definite cases of cerebral oedema (five of which resulted in death). In addition, there have been 10 cases of unexplained deterioration of conscious level but without definite signs of raised intracranial pressure.

In order to obtain controls for the case-control study, monthly notifications have been made to the investigators of all cases of DKA

admitted in England, Scotland and Wales, from 250 paediatricians around the country between March 1996 and February 1998. Around 3200 cases of DKA have been notified. Matched controls will shortly be selected from this group for the cases of cerebral oedema and compared with those in the factors in the presentation and clinical course of case controls.

The investigators are most grateful to all those paediatricians who have notified cases and completed questionnaires.

Funding

The study has received financial support from the British Diabetic Association.

Dr J Edge, Dr M Hawkins, Dr D Dunger, Department of Paediatrics, John Radcliffe Hospital, Headington, Oxford OX3 9DU Tel: 01865 221065 Fax: 01865 220479

Congenital rubella

Background

The National Congenital Rubella Surveillance Programme (NCRSP) was established in 1971 to monitor the effect of immunisation in reducing the incidence of congenital rubella. The selective immunisation of all schoolgirls and of susceptible adult women was supplemented in 1988 with the introduction of the combined measles/mumps/rubella (MMR) vaccine for all children in the second year of life. In November 1994, as part of an attempt to avert a predicted measles epidemic, all 5-16 year olds were offered combined measles/rubella (MR) vaccine. Antenatal screening with postpartum vaccination continues, as does mass immunisation of young children, supplemented from October 1996 by a pre-school MMR booster, but the schoolgirl programme has now ceased.

Objectives

To monitor the effectiveness of the rubella immunisation programme by determining the incidence of congenital rubella in Great Britain and investigating the circumstances surrounding any new cases.

Case definition

Any child up to 16 years of age who, in the opinion of the notifying paediatrician, has suspected or confirmed congenital rubella with or without defects, based on history, clinical, and/or laboratory findings.

Study duration

Congenital rubella was included in the BPSU reporting scheme in January 1990. Reports were previously made directly to the NCRSP.

Analysis

A one-off BPSU survey in 1988 yielded 20 reports, six of which were previously unreported confirmed cases of congenital rubella. Since the beginning of active surveillance in 1990, 103 reports have been made through the BPSU. Fourteen of these reports were from Republic of Ireland or Northern Ireland, and included three children

Table 4 Confirmed congenital rubella births reported to the NCRSP 1971-1997* (England, Scotland & Wales only)

Year of birth	Primary source of notification		Total
	BPSU	Other	
1964-69	0	39	39
1970-79	1	453	454
1980-89	14	320	334
1990-96	32	10	42*
1990	8	4	12
1991	2	1	3
1992	5	2	7**
1993	2	1	3
1994	5	2	7
1995	1	0	1
1996	9	3	12
1997	0	0	0
Total	46	825	871

* The data for recent years are provisional

** Includes one set of triplets

with confirmed congenital rubella (one born in 1989 and two in 1996), eight duplicate or erroneous reports, two children who had been previously reported via another source and one outstanding report; reports from Ireland are followed-up but not included in the NCRSP registry figures. Of the 89 reports from England, Scotland and Wales, 42 are confirmed, previously unreported cases of congenital rubella, seven have already been reported via another source (audiologists, virologists and CDSC) and two remain outstanding. The remaining 40 reports were duplicates (18), reporting errors (18) and two where further information could not be obtained.

Altogether 871 children with confirmed congenital rubella are registered with the NCRSP. Seventy-one (32/45) per cent of those born since the beginning of 1990 (Table 4, previous page) were first reported through the BPSU.

The incidence of congenital rubella in the UK is now very low. Between 1991 and 1995, most of the 19 women giving birth to infected infants either came to Britain as susceptible adults (9), or acquired rubella in early pregnancy abroad (6 - imported cases). However in 1996, following a resurgence of rubella infection in the

community, mainly affecting young males, 12 confirmed cases were reported in England, Scotland and Wales, including eight infants born to British-born women. Only two cases were imported: one Asian woman arrived just two weeks before her baby was born, and one British-born woman acquired infection early in pregnancy while on holiday in Spain.

It is essential that case ascertainment is as complete as possible. Please notify to the BPSU all children suspected of having congenital rubella, whether or not they have the associated typical defects. The researchers are grateful for your effort and cooperation.

*Ms Tookey, Professor C Peckham, Department of Epidemiology and Public Health, Institute of Child Health, 30 Guilford Street, London WC1N 1EH
Tel: 0171 829 8686 Fax: 0171 242 2723 Email: ptooke@ich.ucl.ac.uk
Dr Miller, PHLS, Communicable Diseases Surveillance Centre, 61 Colindale Avenue, London NW9 5EQ Tel: 0171 200 6868*

Haemolytic uraemic syndrome

Background

Haemolytic uraemic syndrome (HUS) is the commonest cause of acute renal failure in children in the United Kingdom. In 1995 the Advisory Committee on the Microbiological Safety of Food (ACMSF) produced a report on Verocytotoxin-producing *Escherichia coli* (VTEC). One of the committee's principal recommendations was that a national prospective surveillance study of HUS should be set up.

HUS is a heterogeneous condition characterised by microangiopathic haemolytic anaemia (fragmented red blood cells), thrombocytopenia and acute renal impairment^{4,5}. HUS has a number of aetiologies, the most important in the UK is Verocytotoxin-producing *E. coli* O157 (O157 VTEC)^{1,7,8,9,10}. O157 VTEC is an emerging infection, it was first identified in the late 1970's and its link with HUS was established early in the 1980's. VTEC of several other serogroups have also been associated with cases of HUS^{1,7}. O157 VTEC does not necessarily cause HUS and infections may be asymptomatic. Two HUS sub-types have been defined; diarrhoea-associated (D+) HUS and a group which lacks a diarrhoeal prodrome, (D-) HUS or 'atypical HUS'^{4,5}. Cases of (D-) HUS have a poorer prognosis and may be familial. VTEC are associated with (D+) HUS.

The fatality rate in cases of HUS may be up to 10% or even higher in institutional settings¹. Chronic renal failure with consequent

human and financial costs is the outcome in another 10% of cases and a further 40% of survivors suffer some renal sequelae. The main reservoir for O157 VTEC is healthy cattle though other animals can carry infection. Humans become infected through the consumption of contaminated foods, particularly minced beef and milk^{1,2,3,11}. However outbreaks of VTEC infection including cases of HUS have been associated with a range of vehicles other than beefburgers and milk, such as yoghurt, cheese, salami, raw vegetables, unpasteurised apple juice and water^{1,6}. Other important transmission routes of VTEC infection are direct contact with animals and person to person spread in families, schools and institutional settings and elsewhere¹.

The BPSU survey of 1986-1989 found an incidence approaching two per 100,000 child population per annum. Reports of VTEC O157 infections have risen since then; only eight cases were confirmed by laboratories in the UK in 1988; 1156 were reported in 1996. The new study will explore effect of this increase in the VTEC O157 on the epidemiology of HUS.

Objectives

- 1 To describe the current epidemiology of HUS in children and to include a measure of severe morbidity and mortality.
- 2 To estimate the proportion of HUS caused by VTEC of all serogroups.

Case definition

A child under 16 years, resident in the UK at time of onset, with all the following:

- 1 Acute renal impairment, including oligoanuria and elevated plasma creatinine for age (plasma urea > 8 mmol/l);
- 2 Microangiopathic haemolytic anaemia (Hb < 10 g/l with fragmented red cells);
- 3 Thrombocytopaenia (platelets < 130,000 x 10⁹/l).

The above may not all be present simultaneously.

in the absence of

Septicaemia, malignant hypertension, chronic uraemia, collagen or vascular disorders.

Study duration

Start February 1997. For three years with annual reviews.

Methodology

- 1 **Local hospital:** Paediatricians should report to the BPSU suspect and definite cases of HUS. When required, guidance on diagnosis can be provided by regional specialists in paediatric nephrology. Faecal specimens and serum samples should be submitted to the local microbiology laboratory. These laboratories will carry out culture tests for *E. coli* O157. The recommended method is to plate specimens on sorbitol MacConkey agar containing cefixime and tellurite and test sorbitol non-fermenting colonies for agglutination with an O157 antiserum. Isolates of *E. coli* O157 should be sent to the Laboratory of Enteric Pathogens, Colindale, together with faecal specimens and sera. In Scotland, all samples should be sent to the Department of Medical Microbiology in Aberdeen. As part of the follow-up after one year a urine sample should be submitted.
- 2 **Laboratory of Enteric Pathogens (Colindale), Department of Medical Microbiology (Aberdeen):** These laboratories will provide confirmation and typing for all VTEC. For *E. coli* O157 subtyping includes phage typing and DNA-based methods where appropriate. Where *E. coli* O157 is not isolated faecal specimens will be examined for the presence of all VTEC. Serodiagnostic tests for antibodies to *E. coli* O157 lipopolysaccharide will also be performed.
- 3 **Communicable Disease Surveillance Centre (CDSC) and Scottish Centre for Infection and Environmental Health (SCIEH):** Paediatricians are asked to report promptly by telephone, all cases of suspected HUS to the CDSC project coordinator (tel: 0181 200 6868 ext 4551) and in Scotland to SCIEH (tel: 0141 300 1100 ext 1118). Initial summary details will then be taken and recorded. A structured questionnaire designed to collect specific epidemiological and clinical data will then be sent to the reporting paediatricians. The paediatricians will be asked to complete the questionnaires and return them to the study coordinator in CDSC (Dr B Adak) or SCIEH (Mrs Mary Locking) at the earliest date possible. Data from the questionnaires will be matched with microbiological data from Colindale and Aberdeen and the information entered onto a database. Follow-up questionnaires will be sent to all paediatricians who have reported twelve months after their initial report of a

case in order to obtain information on longer term morbidity. All data analysis will be conducted by CDSC and SCIEH.

- 4 **Birmingham Children's Hospital NHS Trust:** Drs C M Taylor and D V Milford on advise on clinical aspects of the study on behalf of the British Association for Paediatric Nephrology.

Results

Data is available for the period between the beginning of February 1997 to the end of June 1998. Researchers at the PHLs, CDSC in London and the Scottish Centre for Infection and Environmental Health in Glasgow received 230 reports of HUS cases from collaborating paediatricians in the United Kingdom and Republic of Ireland.

The geographical distribution of cases is shown in Table 5. The reporting of HUS through the BPSU has been designed to complement surveillance of Verocytotoxin producing *Escherichia coli* O157 (VTEC O157) infection. One of the most interesting features to emerge from the current surveillance scheme is the unexpectedly high levels reporting of childhood HUS in the South Thames region, given that this region had the lowest rates of reported VTEC O157 infection in the UK during 1997. Surveillance data from the UK, Europe and North America has shown that there are large regional variations in the geographical distribution of VTEC O157 infection within countries. In a number of countries it has been noted that there are higher rates of infection in rural areas. This is an aspect of the distribution of childhood HUS that will be examined in more detail as the study progresses.

Table 5 Geographical distribution of reported cases of HUS in the UK and Republic of Ireland.

Region/Country	Reported Cases
Scotland	23
Northern Ireland	2
Ireland	11
Anglia & Oxford	13
North Thames	19
North West	27
Northern & Yorkshire	24
South Thames	28
South & West	34
Trent	24
West Midlands	22
Wales	7
Total	234

These data are provisional.

A number of cases reported during the study were found to be involved in outbreaks of VTEC O157 infection. Investigations into these outbreaks have produced some interesting findings which highlight how epidemiology of VTEC infection is evolving. Some of these incidents are discussed below.

In Spring 1997, an infant from London was admitted to hospital with HUS. Investigations revealed that the boy had visited an open farm a few days before he became ill. In total three cases were identified with links to the farm, all were children. A detailed investigation of the farm was conducted and a number of the livestock were found to be excreting the outbreak strain of VTEC O157. The Department of Health convened a specialist group to consider the public health issues resulting from children visiting open farms. The Health and Safety Executive have since produced guidelines for farmers who operate open farms and for teachers who supervise and organise farm visits.

Heavy rains before and during the 1997 Glastonbury Festival resulted in the site becoming a "swamp". Following the festival seven cases of VTEC O157 were reported to CDSC from a number of sources including a paediatrician who was treating a young girl with HUS. Subsequent investigations revealed no common food eaten by all the cases, however cattle from a herd that had been grazing on the site a few weeks before the start of the festival were found to be excreting the outbreak strain. Studies carried out by the Centre for Applied Microbiological Research at Porton Down have since shown that these organisms can persist in viable form in mud cores for a period of months.

In the summer of 1997, a child from the North West of England was reported as a case of clinically confirmed HUS. Investigations carried out by the local Consultant in Communicable Disease Control revealed that the child had recently returned from a holiday in rural France. The boy had consumed unpasteurised milk and had had contact with farm livestock. In recent years there has been a rising trend in the number of cases of VTEC O157 infection associated with foreign travel.

In Spring 1998, five children from the South of England were admitted to hospital following a children's birthday party, one of them was reported as a clinically confirmed case of HUS. All of the children were found to have consumed cold drinks made with tap water. Microbiological investigations demonstrated that tap water in the house where the party took place was contaminated with the outbreak strain of VTEC O157. The water came from an untreated private supply.

Also in Spring 1998, an HUS case was reported from a West Country hospital. The child was confirmed as having VTEC O157 infection.

Investigations carried out by the local Environmental Health Department revealed that the child had eaten cheese made from unpasteurised milk. Further investigations demonstrated that unopened batches of cheese obtained from the producer were contaminated with VTEC O157. As a result action was taken to prevent the sale of cheese made by this producer. This was the second incident in the UK where VTEC O157 infection was found to be acquired through the consumption of cheese made from unpasteurised milk.

Discussion

In recent years there have been large outbreaks of VTEC O157 infection which were shown to be associated with the consumption of meat products. A great deal of attention has been focused on the dangers of consuming undercooked burgers and on the problems that may arise from poor hygiene standards food retailers. However it needs to be borne in mind that VTEC can be transmitted in a number of ways. Illness can be acquired through contact with livestock or infected people, including asymptomatic excretors, as well as through the consumption of contaminated products including: cold cooked meats; undercooked minced meat dishes; unpasteurised dairy products; salad vegetables; fruit juices; untreated water. Recent follow-up investigation of children with HUS have demonstrated that disease is contracted in an increasing number of ways and that young children are particularly vulnerable to the most severe effects of VTEC infection.

The researchers would like to emphasize that it is important to complete the BPSU orange card in addition to initial telephone reports.

Dr C M Taylor, Dr D V Milford, Birmingham Children's Hospital NHS Trust, Laboratory of Enteric Pathogens, Ladywood Middleway, Birmingham B16 8ET Tel: 0121 454 4851 ext 6120

Dr B Rowe, Dr GK Adak, Dr S O'Brien, Central Public Health Laboratory, 61 Colindale Avenue, London NW9 5HT Tel: 0181 200 6868 ext 4551 Fax: 0181 200 7868 Email: BAdak@phls.co.uk*

Professor T H Pennington, Dept of Medical Communicable Disease Microbiology, Aberdeen Royal Hospitals NHS Trusts, Forester Hill, Aberdeen AB9 2ZB Ms M Locking, Scottish Centre for Infection and Environmental Health, Clifton House, Glasgow G3 7LN Tel: 0141 300 1100 ext 1118*

** References (1-10) available from principal researcher (in bold) on request.*

Hepatitis C virus (HCV) infection

Background

HCV is the major cause of post-transfusion and community acquired nonA- nonB hepatitis. Infection in HCV has the ability to persist in the host in the majority of cases, it may lead to chronic liver disease and hepatocellular carcinoma. However, there is little information on the natural history of HCV infection in children.

HCV can be transmitted from mother to child, but the risk of vertical transmission appears to be low (1-10%) unless there is co-infection with HIV. The main recognised routes of transmission are transfusion of infected blood or blood products, organ transplantation, intravenous drug use and other situations where percutaneous inoculation may occur (needlestick injuries, tattoos). Transmission between family members has been reported, and sexual transmission may occur, though conclusive evidence of this is lacking. Viral inactivation of clotting factor concentrate started in the UK in

1984, but did not extend to all blood products; routine screening of blood, blood products and organ donors for HCV started in September 1991. Children at high risk of being infected with HCV prior to 1991 include those who received bone marrow transplants or multiple blood transfusions, and those with haemophilia. Screening all children at risk has not been undertaken systematically, and paediatricians from a range of specialities may be involved in the management and follow-up of children who have been identified.

Objectives

- 1 To estimate the prevalence and distribution of known paediatric HCV infection in the UK and Republic of Ireland;
- 2 To look at patterns of presentation according to mode of transmission (infected blood products/organ transplantation or mother to child);
- 3 To describe the current management by risk group;
- 4 To investigate the natural history of HCV infection in children with a known date of infection.

Case definition

- 1 Any child who is HCV antibody positive (including any child under 18 months of age born to an HCV infected woman and any older child with definitive HCV infection).
- 2 Any child who is positive for HCV by RNA PCR.

In 1998 the surveillance strategy changed, since then only children infected with HCV need to be reported and it was not necessary to report children born to HCV infected mothers.

Study duration

March 1997 - March 1999

Methods

Reporting paediatricians are asked to complete a surveillance form shortly after the reporting card is received by the BPSU, and a follow-up form will be sent annually thereafter.

Surveillance of paediatric HCV is running in parallel with surveillance of paediatric HIV and is conducted by the same group. If a paediatrician has already reported a child with HIV infection who also has HCV, a new report should be made for the HCV. For new cases of dual infection, both boxes on the orange card should be ticked. Once it is established that the child has been reported to both studies, follow-up will be coordinated to avoid duplication.

Results

To May there have been 608 notifications, and 418 reports returned meeting the case definition. There have been 41 duplicate reports and 28 cases reported in error. The initial status of the remaining 121 notifications has yet to be determined.

Of the 418 valid reports, 159 children are infected; 34 (21%) were born to an infected mother, and 118 (74%) received contaminated blood products. Two children had organ transplants and five were

infected from other sources (two needlestick injuries, two with uncertain risk factors and one intravenous drug user).

There are 259 children of indeterminate infection status born to HCV infected mothers but not necessarily infected, and these will be followed-up during the course of the year.

Of the 293 children born to HCV infected mothers, 41 came from London and the South East, 129 from the rest of England and Wales, four from Wales, 20 from Scotland and 99 from Republic of Ireland. Of the other 125 children, 25 were from London and the South East, 60 from the rest of England, four from Wales, 20 from Scotland and 16 from Republic of Ireland. Fourteen vertically infected children are under two years of age, and six are aged between three and five years. The older children at risk of vertical transmission have presumptive diagnoses as their mothers were found to be infected after delivery. Intra-familial transmission may be a possibility. Six of the other infected children are between three and five years of age and the rest (119) are six or over. Twenty-two mothers were co-infected with HIV. Three of their children have HCV and HIV and two have HIV infection only. Only eight of the 159 infected children were reported to have any symptoms, four with hepatomegaly, two with signs of hepatitis and two with jaundice. Liver biopsies have been carried out on 47 (30%) of infected children. Thirty-three have mild, nine moderate and one severe hepatitis.

Twenty-seven children have received interferon therapy, (two vertically infected, 25 blood products infected). Biopsy results showed six had moderate and 11 mild hepatitis. The other children who received interferon therapy were haemophiliacs and so had not had liver biopsies.

Hepatitis C genotyping is being carried out on infected children from whom virus is raiseable with PCR. This has been undertaken on 49 children.

Conclusions

HCV in children is found all over the British Isles, but there are particularly large numbers of children born to HCV infected mothers in Dublin and Liverpool.

Surveillance of infected children only will continue for another 12 months. Long-term follow-up of infected children is being discussed with Communicable Disease Surveillance Centre and Scottish Centre for Infection and Environmental Health.

Only 17% of children have received interferon therapy, and none have had ribavirin. Treatment trials are urgently needed to assess their efficacy in children.

Dr D Gibb, Ms P Neave, Ms P Tooke Department of Epidemiology and Biostatistics, Institute of Child Health, 30 Guilford St, London WC1N 1EH. Tel: 0171 813 8396 Fax 0171 242 2723

Collaborators: Dr M Ramsay, PHLS, Communicable Disease Surveillance Centre, National Blood Authority, Dr D Goldberg, Scottish Centre for Infection and Environmental Health/Scottish National Blood Transfusion Service

HIV/AIDS infection in childhood

Background

National surveillance of paediatric HIV infection and AIDS began in 1986 in order to monitor the incidence and prevalence of paediatric infection. It is based on a combination of paediatric, obstetric and laboratory reporting schemes.

Most cases of paediatric HIV infection and AIDS are children born to women infected with HIV and it is now possible to establish the infection status of congenitally exposed children by three to four months of age. Interventions such as antiretroviral treatment for the pregnant woman and her newborn infant, delivery by caesarean section and the avoidance of breastfeeding have dramatically reduced transmission rates. Furthermore, prophylaxis for infected infants can reduce the incidence of pneumocystis carinii pneumonia (PCP), a major cause of HIV-related morbidity and mortality in the first year of life. However, in the UK paediatric HIV is still most commonly recognised only when the child, or a member of their family, becomes ill. Overall less than one in four infected women are diagnosed before their baby's birth and detection rates for previously undiagnosed infection in pregnancy are very low, only 15% in 1996¹. This compares poorly with detection rates reported in other parts of Europe and the United States and it is vital that appropriate antenatal testing policies are implemented and monitored in the UK, as recommended in the recently published intercollegiate guidelines², so that HIV-infected women can be offered treatment and advice, vertical transmission rates can be minimised and infected infants receive optimum care.

Objective

The surveillance of paediatric HIV infection and AIDS in the United Kingdom and the Republic of Ireland.

Case definition

Any child less than 16 years of age who has AIDS, or is HIV antibody positive, or with positive virus culture, polymerase chain reaction (PCR) or antigen detection, or any other laboratory marker of HIV infection. Also any child born to a woman known to be HIV infected at the time of that child's birth regardless of the child's infection status.

Study duration

The survey began in June 1986 and reviewed annually.

Analysis

By the end of January 1998 there had been 1285 reports through the BPSU. Seven hundred and fifty-three children born to HIV infected women, and therefore at risk of vertical transmission, were reported (Table 6), together with 48 children who were infected in the course of treatment for haemophilia, 22 infected through blood transfusion and four for whom the transmission route cannot be established. One hundred and ninety-eight of the remaining reports were duplicates, and there were 220 reporting errors or cases where the paediatrician was unable to remember the child they had reported. Forty reports are still being investigated.

Table 6 Infants born to HIV infected women, and confirmed cases of paediatric HIV infection (notified by 31 January 1998)

Transmission route (actual or potential)	BPSU Reports	Reports from other sources	Total
risk of vertical transmission	753	568	1321
haemophilia treatment	48	221	269
blood transfusion/products	22	17	39
other/not yet established	4	16	20

A further 822 reported cases have been identified from other sources (see Endnote) including 568 children born to HIV infected women, 221 children with haemophilia, 17 infected through blood transfusion and 16 where the route of transmission is at present unclear. Data from all sources are combined each quarter and form the basis of the national surveillance of HIV infection and AIDS in children, with UK summary tables appearing on a quarterly basis in the Communicable Disease Report (England, Wales and Northern Ireland) and ANSWER (Scotland).

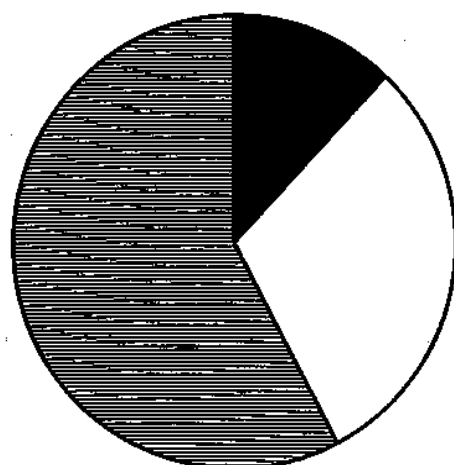
All reporting is voluntary and confidential. Almost all of the surviving young people infected during the course of treatment for haemophilia are now over 16 years old, and their follow-up is undertaken by the UK Haemophilia Centre and the PHLS AIDS and STD Centre. All other children are followed-up yearly to monitor their clinical and immunological status and for those at risk of vertical transmission, to determine their infection status. By the end of January 1998, among the 1321 children born to HIV infected mothers (Table 7), 497 had confirmed infection, 348 were then of indeterminate status and 476 were known to be uninfected. Transmission rates cannot be estimated from these data as there is a bias towards the reporting of symptomatic

Table 7 Infection status of children born to HIV infected women (notified by 31 January 1997)

HIV infection status	Thames Regions	Rest of England, Wales, Northern Ireland,	Scotland	Republic of Ireland	Total
AIDS	207	48	19	18	292
HIV infection (not AIDS)	150	26	15	14	205
indeterminate	248	51	35	14	348
uninfected	218	54	120	84	476
TOTAL	823	179	189	130	1321

Figure 4 Vertically infected children born in the UK and developing AIDS: data to January 1998

At what stage were maternal infections diagnosed?



CDSC, SCIEH & ICH(L)

Source: Voluntary confidential reporting by Obstetricians (RCOG), Paediatricians (BPSU/RCPCH) and laboratories (CDSC/PHLS)

children. One hundred and thirty (10%) of these children had been reported from the Republic of Ireland, 189 (14%) from Scotland, 823 (62%) from the Thames regions and 179 (14%) from the rest of England, Wales and Northern Ireland.

Two hundred and ninety-two children infected through mother to child transmission were reported to have developed AIDS by the end of January 1998 (Table 7). Of these 192 were born in the UK and it is possible to explore the timing of the diagnosis of maternal infection in this group (Figure 4). Only 15 women (8%) were reported to have been diagnosed before they became pregnant and 8 (4%) during the antenatal period. The majority 111 (58%), appear not to have known they were infected and not to have been diagnosed until their child developed AIDS. These women would not have been able to take advantage of interventions that could have reduced the risk that their child would be infected. Women in a similar situation now would also be unable to take up therapies that could improve their own health.

Growing numbers of both infected and uninfected children have had perinatal exposure to antiretroviral therapy and mechanisms are being established for monitoring both short and long-term outcomes in such children, in order that any unexpected or unusual sequelae of treatment can be recognised as early as possible.

Thanks go to all members of the RCPCH, particularly those paediatricians who have reported cases and completed questionnaires, for their continued support and diligence.

Funding

This study is funded by AVERT (AIDS Education & Research Trust), and additional support is received from the collaborating institutions and the Medical Research Council, which funds the routine collation of data each quarter and transfer to national surveillance centres.

Mother's HIV infection diagnosed:

■ before pregnancy:	15 (7.8%)
■ during pregnancy:	8 (4.2%)
□ after child's birth but before AIDS developed:	58 (30.2%)
▨ when child developed AIDS:	111 (57.8%)

TOTAL 192 CHILDREN

Endnote

Additional sources include: an obstetric reporting scheme run under the auspices of the Royal College of Obstetricians and Gynaecologists; reports to the UK Haemophilia Centre; laboratory reports to the Public Health Laboratory Service AIDS Centre at the Communicable Disease Surveillance Centre, and the Scottish Centre for Infection and Environmental Health; reports made directly to the coordinating centre at the Institute of Child Health in London.

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- 2 Reducing mother to child transmission of HIV infection in the United Kingdom. Royal College of Paediatrics and Child Health 1998. Intercollegiate Working Party for Enhancing Voluntary Confidential HIV Testing in Pregnancy (Royal Colleges of General Practitioners, Midwives, Nursing, Obstetricians & Gynaecologists, Pathologists, Paediatrics & Child Health and Physicians; Public Health Laboratory Service; Faculty of Public Health Medicine, Directorates of Public Health for North & South Thames).

Ms P Tookey, Miss T Duong, Ms J Masters, Department of Epidemiology & Biostatistics, Institute of Child Health, 30 Guilford St, London WC1N 1EH
 Tel: 0171 829 8686 Fax: 0171 242 2723 Email: ptookey@ich.ucl.ac.uk
 Dr A Nicoll, PHLS CDSC, 61 Colindale Avenue, London NW9 5EQ
 Tel: 0171 200 6868, Email: ANicoll@phls.co.uk
 Dr D Goldberg, SCIEH, Clifton House, Glasgow G3 7LN
 Tel: 0141 300 1100

Invasive *Haemophilus influenzae* infection

Background

In October 1992 *Haemophilus influenzae* type b (Hib) conjugate vaccines were introduced for routine immunisation of infants in the United Kingdom (UK) and the Republic of Ireland (ROI). The acceptance and uptake of vaccine has been high and the incidence of Hib disease has fallen dramatically.

In September 1992 the BPSU included invasive *H. influenzae* infection occurring after Hib immunisation in its reporting scheme and in November 1995 widened the case definition to include all children with invasive *H. influenzae*, regardless of vaccination status. Following the dramatic decline in invasive *H. influenzae* that was seen following the introduction of Hib immunisation in 1992, the surveillance mechanism has identified children in whom vaccination is unsuccessful as worthy of further immunological evaluation and follow-up and allowed preliminary estimates of vaccine effectiveness to be made. The continuation of surveillance is addressing the important issue of the duration of protection provided by primary immunisation. Protection against Hib disease is required until children are at least five years of age by which time natural immunity has usually developed. The absence of a second year Hib booster in the UK and ROI (most other countries include such a booster) therefore necessitates careful monitoring of the programme. The widening of the case definition aims to ensure complete case ascertainment and to identify pockets of continuing transmission. Such information will aid in targeting control measures and deciding future vaccination strategies.

Objectives

To identify cases of invasive *H. influenzae* disease occurring in children regardless of their vaccination status enabling:

- 1 estimation of the effectiveness of Hib conjugate vaccines in British and Irish children;
- 2 determination of the importance of disease due to non type b *H. influenzae*
- 3 documentation of host factors and the clinical presentation of the disease, and in cases of vaccine failure, the collection of acute and convalescent concentrations of Hib antibody.

Paediatricians are asked to report cases as soon as possible, preferably by telephone, if *H. influenzae* is isolated from a normally sterile site in a child under 16 years of age irrespective of his/her vaccination status. Telephone reporting is needed because a sample should be sent promptly to the PHLS *Haemophilus* Reference Laboratory at the John Radcliffe Hospital, Oxford, where the serotype of the organism is determined by standard microbiological techniques and capsular genotyping using a polymerase chain reaction (PCR) technique. In cases of vaccine failure, attempts are made to collect acute and convalescent specimens of serum.

Case definition

Definite: A child between 0-16 years of age in whom *H. influenzae* is cultured from a normally sterile site eg. CSF / blood / joint aspirate. The child should be notified regardless of vaccination status.

Examples of invasive diseases include meningitis, pneumonia, bacteraemia, epiglottitis, septic arthritis and osteomyelitis.

Probable: Where antibiotics are administered prior to cultures being taken, the clinical disease is compatible with invasive Hib disease (as listed above) and either:

- Hib antigen is detected in fluid from a normally sterile site or
- A four-fold rise in Hib antibody between acute and convalescent serum specimens is recorded.

True vaccine failure: the occurrence of invasive Hib disease after three doses of vaccine, or more than one week after two doses given in the first year of life, or more than two weeks after a single dose given to a child over twelve months of age.

Apparent vaccine failure: Hib disease that occurs after vaccination has been given but before protection could be reasonably expected to develop, for example, disease occurring after one dose in the first year of life.

Study duration

The study began in September 1992 and is reviewed annually.

Analysis

By April 1998, 548 reports had been made including 405 cases in vaccinated and 143 in unvaccinated children. 113 cases represented true vaccine failures (TVF), 69 apparent vaccine failures and 13 were possible vaccine failures (protective course of vaccination received, isolate of *H. influenzae* obtained but not typed). Amongst vaccinated children there were 116 with invasive disease due to non capsulate strains of *H. influenzae* and 28 with non b capsulate strains, mostly type f. Sixty six reports did not meet the case definition.

One hundred and three of the 113 TVF were vaccinated in the first year of life: 92 received three doses and 11 received two doses. Ten were vaccinated when older than 12 months of age. Of those UK born and vaccinated in the first year of life, 22 developed disease between five and 11 months of age, 36 between 12 and 23 months of age, 22 between 24 and 35 months of age, eight between 36 and 47 months of age, three between 48 and 59 months of age and one between 60 and 71 months of age. Surveillance has therefore allowed the following point estimates of vaccine effectiveness to be made (three doses in infancy): 99% (95%CI 98-99%) for children aged 5-11 months, 98% (97-98%) for those aged 12-23 months, 96% (94-97%) between 24-35 months of age, 97% (94-99%) between 36-47 months of age and 93% (79-99%) for those aged 48-59 months of age. For the whole period from five to 59 months of age, the estimate is 98% (98-99%).

In the ROI, numbers of cases in each age class together with point estimates of efficacy (for three doses) and 95% CI (assuming 75% vaccine coverage) are as follows: 8-11 months of age - 0 (100%, 94-100%), 12-23 months of age - 4 (96%, 89-99%), 24-35 months - 4 (83%, 57-96%) 36-47 months of age - 1 (89%, 38-100%) and 48-59 months of age - 0. For the whole period the estimate is 95% (91-98%).

The modes of presentation and associated medical and immunological conditions amongst the cases of TVF are detailed in Table 8. Overall 46 (41%) were shown to have an associated condition. There have been three deaths.

Convalescent sera were available in 103 cases of TVF. Thirty-three (32%) demonstrated a poor antibody response to disease (<1 µg/ml), necessitating a booster dose of vaccine.

The majority of *H. influenzae* isolated from unvaccinated children have been non capsulate strains (63/143) with a predominance of neonatal disease, especially in premature infants. Hib has been isolated from 32 children, 19 (59%) old enough to have been fully vaccinated.

Table 8 Presenting illness and associated conditions of true vaccine failures (TVF) Sept 1992 - April 1998

Presenting illness	Associated condition		
Meningitis	65	Prematurity	11
Epiglottitis	22	Cromosomal abnormality	4
Bacteremia	15	(includes 3 Down's syndrome)	
Cellulitis	5	Malignancy	4
Pneumonia	3	Dysmorphic	3
Septic arthritis	3	Cyclical neutropenia	1
		Immunoglobulin deficiency	30

Comment

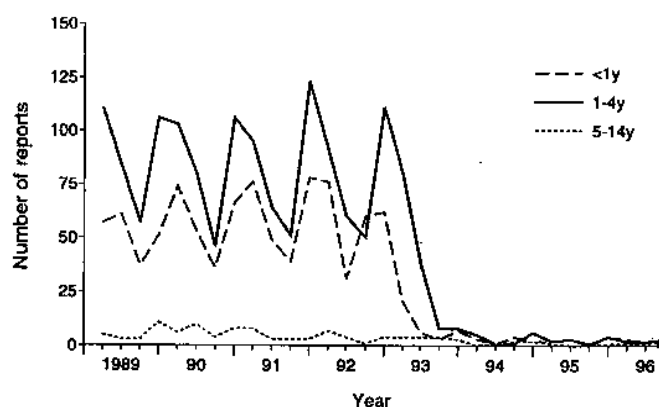
This surveillance continues to demonstrate high levels of protective efficacy of the Hib conjugate vaccine PRP-T (ActHib) when given at 2, 3 and 4 months of age in the UK. In the ROI accurate vaccine coverage figures are not available and the relatively small population size results in wide confidence intervals around estimates. It is generally believed that vaccine coverage in the ROI is only moderate (eg 75%) yet the decline in disease incidence has been dramatic (>92%), illustrating the impact of Hib conjugate vaccines on herd immunity.

Should vaccine protection wane due to the absence of a booster dose together with the reduction in boosting by pharyngeal carriage of Hib, an excess of cases should become apparent in older children. Currently, point estimates of efficacy remain very high up to and including the fifth year of life, but surveillance must continue to ensure that a booster dose will not be required.

In terms of clinical practice it is reasonable to seek an underlying host abnormality in cases of vaccine failure and also in cases of invasive disease due to non capsulate *H. influenzae*. Measurement of

convalescent Hib antibody levels following vaccine failure provides guidance on further doses of vaccine. The most frequently identified associated clinical condition has been prematurity. Immunogenicity studies of Hib vaccines in those born prematurely suggest that indeed this group might be at greater risk of vaccine failure. However, this study has shown that as a group they are not represented in excess of the numbers expected. These data are very important as they do not support a change in vaccination policy for these specific individuals, a conclusion one might otherwise draw from the immunogenicity studies.

Figure 5 Laboratory reports of *H. influenzae* type b (bacteraemia and meningitis) England and Wales 1989 - 1996 (3rd quarter) Immunisation started in 1992



Following the impressive reduction in Hib disease (Figure 5) the majority of cases now reported to the study are due to non type b *H. influenzae* i.e. not vaccine preventable, a distinction important in maintaining public confidence in this vaccine. Non capsulate strains represent most of these isolates and appear to be associated with neonatal disease. There is no evidence of an increase in non type b *H. influenzae* as a result of widespread Hib vaccination.

Type b disease continues to occur however, and although the majority of cases are in vaccinated children most of those unvaccinated with Hib disease were of an age that a complete course of Hib vaccination should have been given. High vaccine uptake remains vital if this disease is to be eliminated.

We are most grateful for the collaboration of paediatricians, microbiologists and public health physicians in this study.

Dr P Heath, Professor R Maxon, Dr M Slack, Oxford Vaccine Group and PHLS Haemophilus Reference Laboratory, John Radcliffe Hospital, Oxford OX3 9DU Tel: 01865 221068/220859 Fax: 01865 220479

Email: paul.heath@paediatrics.oxford.ac.uk

Dr J Fogarty, Dept of Public Health Medicine, Merlin Park Hospital, Galway, Republic of Ireland Tel: 00353 91 751131

Dr M Ramsay, PHLS Communicable Disease Surveillance Centre, 61 Colindale Avenue, London NW9 5EQ Tel: 0181 200 6868

Scottish Centre for Infection and Environmental Health, Clinton House, Glasgow G3 7LN

Neonatal meningitis

Background

Between 1985 and 1987 the Karim Centre for Meningitis Research carried out a survey to determine, over a two year period, the incidence of meningitis in children aged under one year. At the time no country-wide survey had ever been completed. The incidence of neonatal meningitis was 0.32 per 1000 live births and the principal infecting bacteria were Group B β haemolytic streptococci, *Escherichia coli* and *Listeria monocytogenes*. Data from the study showed that 50% of neonates had been treated with a regimen based upon chloramphenicol and 50% upon aminoglycosides. The diagnosis was usually based on a positive culture from the cerebrospinal fluid (CSF), cell counts in the CSF and the clinical picture. Over 30% of the babies who survived have an identifiable neurodevelopmental problem at five years of age.

Over the intervening years paediatric practice in diagnosis and treatment of neonatal meningitis has changed. Lumbar punctures are now often omitted from routine infection screens and they may also be omitted when the baby has serious signs indicative of meningitis. The first line treatment with a combination of a penicillin and chloramphenicol or an aminoglycoside has been replaced by a combination of ampicillin and a third generation cephalosporin and it is suggested there is also increasing use of steroids and immunoglobulins in this age group.

Objectives

To determine the incidence, mortality, diagnostic procedures, principal infecting organisms and treatment of meningitis in the newborn period. This is to revise current knowledge of the disease, its diagnosis and treatment, which was first surveyed over 10 years ago. The population of children identified by the study will subsequently be examined at five and nine years of age to determine long-term morbidity after modern treatment.

Case definition

Meningitis in newborn babies, including those born preterm, of 28 days of age or less, as diagnosed by local procedures. Those cases where diagnosis was by clinical signs and not proven by CSF analysis and culture, but treated as neonatal meningitis by the paediatrician were included. Cases of viral meningitis were included. Babies where meningitis was diagnosed at autopsy were included. Cases with neural tube defects were excluded.

Paediatricians and microbiologists were asked to provide clinical and laboratory details on notified cases and we asked for a sample of CSF to be supplied if available.

Study duration

The study concluded in December 1997 after 18 months.

Analysis

The Karim Centre has received from the BPSU 459 notifications of suspected or proven neonatal meningitis during the 18 month study period. Of these cases, 93 have been excluded for a variety of reasons, including duplication, cases outside the stated definition and cases notified in error. At the time of writing completed questionnaires have been received from paediatricians on 309 of the 366 cases which fall within the case definition; a completion rate of 85%. The investigators are confident, after discussion with individual paediatricians, that data on the remaining 57 cases will be returned in due course. Of the 310 questionnaires sent to consultant microbiologists, 251 (81%) completed questionnaires have been received.

The mean age at diagnosis was ten days and slightly more boys (55%) than girls (45%) were affected. Bacterial meningitis accounted for 53% of cases, viral for 7%, and yeasts (*Candida*) for 1%. In 34% of cases CSF WBC count raised but no organism was grown on culture. The remaining 5% of cases were diagnosed on clinical evidence alone. The most common bacteria isolated from the CSF were Group B β hemolytic streptococci (49%), *Escherichia coli* (18%) and *Listeria* (6%). Commonly used antibiotics were cefotaxime, penicillin, ampicillin and gentamicin, while 9% of the babies were treated with steroids.

At the time of completion of the questionnaire by the paediatricians 14% of the babies remained in hospital, 78% had been discharged and 8% had died.

Comments

While these data remain preliminary and no in depth analysis can be carried out until details have been collected on all reported cases, it appears that the incidence of neonatal meningitis remains similar to that reported by us ten years ago. Deaths from the disease have declined since our first survey but the interesting question of a possible concomitant change in morbidity will not become clear until follow-up. The researchers are currently determining by a variety of methods the likely extent of missed cases across the British Isles in an attempt to ensure that data collection is complete.

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Mrs S Halket, Dr D Holt, Karim Centre for Meningitis Research, Queen Charlotte's & Chelsea Hospital, London W6 0XG

Tel: 0181 740 3924 Fax: 0181 741 1838. Email: dholt@mpc3.rpms.ac.uk

Pyridoxine dependency

Background

Pyridoxine dependency is a rare, but treatable, recessively inherited cause of seizures starting in early childhood. Since its description in 1954 less than 50 definite cases have been described in the published literature, all in case reports or small hospital based series. No large scale or population based study has ever been reported and the incidence and prevalence of the condition are essentially unknown.

Up to one third of reported cases present atypically with, for example, an onset of convulsions after the neonatal period (up to two years) or a transient response to standard anticonvulsants. Other clinical complications occur, such as abdominal symptoms, early visual agnosia, structural changes in the nervous system, or seizures provoked by intercurrent infections, but their frequency is unknown. With these varied presentations, the condition is likely to be under-recognised. The outcome for psychomotor development is reputed to be poor even in cases treated early, but this is debatable as no formal study has been undertaken. The reported required dose of pyridoxine for individual patients varies between 10 and 1000 mg daily, but it is not usually changed with age and the optimal dose is unknown. Individual case reports suggest a disorder of GABA metabolism may be at fault but neither the metabolic nor the genetic abnormality is identified.

Objectives

This study is to:

- 1 determine the prevalence of definite or possible pyridoxine dependent seizures in children under 16 years of age;
- 2 prospectively study the incidence in children under five years of age;
- 3 define the clinical presentation, natural history, and clinical management of pyridoxine dependency.

Case definition

Pyridoxine dependent seizures: recurrent seizures that respond to pyridoxine, or any child receiving pyridoxine for suspected pyridoxine dependent seizures.

Definite cases were defined as neonates, infants or young children with recurrent (that is, two or more) seizures of any type, including infantile spasms, that cease within seven days of the administration of oral pyridoxine (usual dose: 30 mg/kg/day, minimum 15 mg/kg/day, maximum 1000 mg/day) or within 30 minutes of intravenous pyridoxine (usual dose 100 mg, minimum 50 mg), that recur when pyridoxine supplementation is withdrawn, and that cease again when pyridoxine is given as above.

Possible cases were defined as above, but without an attempt to withdraw pyridoxine.

Reporting paediatricians were asked to include cases in whom there were other suspected or definite causes of seizures, to ensure complete reporting.

Study duration

September 1995 - October 1997

Results

Reports of 47 cases were received by the BPSU. Twenty-four more reports were obtained via other sources including seven described by a specific study in Northern Region, two presenting to the investigator and one adult. Two questionnaires, both of likely negative cases, have yet to be returned. There were six duplicate notifications.

During the study another group of cases were defined as having "probable" pyridoxine dependency. These were neonates with seizures which stopped after a single dose of pyridoxine but later recurred and again responded to pyridoxine which was then continued.

Including data from all sources 13 definite, ten probable and ten possible cases were notified. The prevalence of definite and possible cases in children less than 16 years of age at the end of the study was 1:620,000 and the birth incidence 1:700,000. Including possible cases these figures became 1:450,000 and 1:350,000 respectively. These should be regarded as minimum incidences.

A further five cases presented with infantile spasms responsive to pyridoxine. One of the "possible" cases whose seizures were controlled from the neonatal period also presented at six months with infantile spasms that were controlled with an increased dose of pyridoxine.

Fifteen cases were notified who did not fulfil the case definitions. Some of these had neonatal seizures responsive to pyridoxine that did not recur on withdrawal, while others had recurrent afebrile seizures despite continuing pyridoxine.

The other notifications were either revised, or made in error, or lost as no contact could be made with the locum consultant who had made notification.

There were unexpected geographic variations, including relatively few cases from Greater London. An increased number of possible cases were born during the study period. These findings suggest under-reporting from some areas and that the presence of the condition on the BPSU card heightened awareness.

The presenting features were similar to those previously described. Some had features of birth asphyxia and/or neonatal encephalopathy. Abdominal distension, vomiting, temperature variability and grunting respiration also occurred in some neonates. Those children with

markedly delayed diagnoses had poor outcomes with four limb cerebral palsy and severe learning difficulties, whereas those with early diagnoses and treatment had mild or no disabilities.

Conclusions

Pyridoxine dependent seizures are rare. There are unexplained variations in geographic origin. Pyridoxine responsive seizures, including infantile spasms, also occur in young children.

Cases can be misdiagnosed as birth asphyxia with hypoxic ischaemic encephalopathy. A high index of suspicion is necessary to avoid preventable disability.

Dr P Baxter, Consultant Paediatric Neurologist, Ryegate Children's Centre, Sheffield Children's Hospital, Sheffield S10 2TH

Tel: 0114 267 0237 Fax: 0114 267 8296 Email: p.s.baxter@sheffield.ac.uk

Progressive intellectual and neurological deterioration in children

Background

BPSU surveillance for progressive intellectual and neurological deterioration (PIND) in children (including Creutzfeldt-Jakob Disease) began in May 1997. Paediatric PIND covers an important group of conditions, which have not been investigated epidemiologically in the UK. The recent appearance of new variant CJD (nvCJD) in patients as young as 16 years of age or less suggested the possibility that nvCJD is occurring in children¹. Either the detection of nvCJD in UK children, or the demonstration that it is not occurring, would be an important finding for paediatrics and public health. The presentation of nvCJD is not typical of classical CJD, and therefore the clinical presentation of any cases in children is difficult to predict. The strategy is to detect suspected cases by looking at a broader group of conditions. This group needs to be large enough to include all possible cases of nvCJD, hence surveillance is being undertaken for a range of presentations under a combined term – Progressive Intellectual and Neurological Deterioration. An Expert Neurological Advisory Group consisting of six senior paediatric neurologists supports the research team by meeting quarterly, discussing (anonymously) all newly notified cases, and classifying them according to study categories. The BPSU surveillance is being coordinated with the National CJD Surveillance Unit in Edinburgh and the Public Health Laboratory Service.

Objective

To carry out active prospective surveillance of UK children with paediatric neurological conditions (including those with specific diagnoses) defined by their common presentation – progressive intellectual and neurological deterioration (PIND) – to determine the incidence and distribution of PIND. Cases presenting with PIND are evaluated critically in order to classify them and investigate the possibility that nvCJD is occurring in children.

Case definition

Any child under 16 years of age at onset of symptoms who fulfils all of the following three criteria:

Progressive deterioration for more than three months with
loss of already attained intellectual/developmental abilities
and
development of abnormal neurological signs.

Excluding: static intellectual loss, eg. after encephalitis, head injury or near-drowning.

Including: children who meet the case definition even if specific neurological diagnoses have been made.

Metabolic disorders leading to neurological deterioration.

Seizure disorders if associated with progressive deterioration.

Children that have been diagnosed as having neurodegenerative conditions but who have not yet developed symptoms.

Reporting restricted to: Cases seen in the last month but including those whose conditions began earlier (i.e. including "old cases" of children in follow-up (if seen in that month).

Suspected cases of SSPE should also be reported to the SSPE surveillance project see page 28.

Study duration

May 1997 to April 2000 (three years)

Current status

By the middle of May 1998 a total of 413 children had been reported via the BPSU. Of these:

1. The Expert Group has discussed 233 cases:
 - 120 have been classified as having a recognised cause of PIND;
 - 97 have been classified as meeting the surveillance case definition and are still under investigation;
 - 12 did not strictly fulfil the study criteria for PIND and were not included;
 - four have been classified as Idiopathic Non-CJD;
 - none have been classified as definite, probable or possible nvCJD.
2. Of the remaining 180 notifications not yet discussed by the Expert Group:

121 are currently in the process of being followed up - i.e., still awaiting response to initial contact letter sent to notifying paediatrician, telephone interview/visit arranged but not yet carried out, telephone interview/visit still to be arranged; 59 were not included for various reasons - i.e., child too old for study, reported in error, duplicate report.

Important regional differences have been noted in the incidence of reported PIND cases. Yorkshire has notified the highest number of cases to date (65), and West Midlands the second highest (51). The reasons for this are now being investigated.

Thirty-six different conditions have been reported which are included in the 120 cases classified by the Expert Group as having a recognised cause of PIND (in other words, a definite diagnosis). MPSIIIA (San Filippo) features most frequently - 12 cases. There are nine cases of Tay Sachs, eight Juvenile Batten's, six Sandhoffs, six Late Infantile Batten's and five Pelizaeus Merzbacher cases.

"Yorkshire" and "West Midlands" are BPSU regions.

Comments

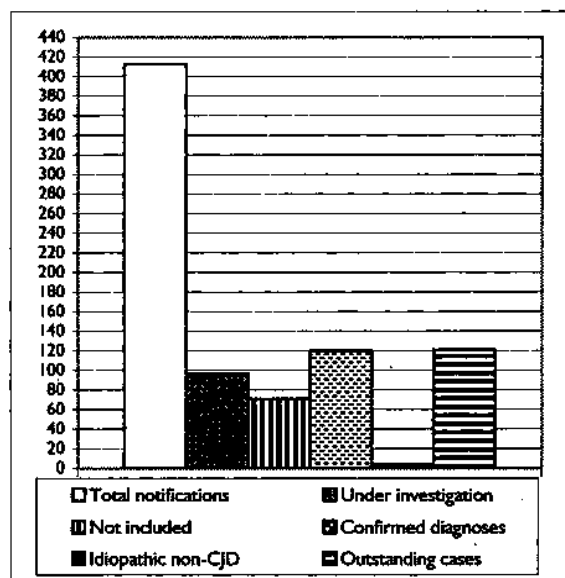
This study has provided an important and unique overview of the epidemiology and clinical picture of childhood neurodegenerative disease in the UK. So far, the survey has not identified any cases nvCJD.

The investigators are very grateful to all paediatricians for supporting this research and for sharing information about their patients.

Reference

Will RG, Ironside JW, Zeidler M et al. A new variant of Creutzfeldt-Jakob Disease in the UK. *Lancet* 1996; 347: 921-5

Figure 6 Current Status



Dr C Verity, Consultant Paediatric Neurologist (Principal Investigator), Addenbrooke's NHS Trust, Hills Road, Cambridge, CB2 2QQ

Tel: 01223 216662 Fax: 01223 242171

Ms G Devereux, Research Nurse, Mrs L. Stelltano, Research Administrator, c/o Paediatric Administration Office, Box 45, Addenbrooke's NHS Trust, Hills Road, Cambridge, CB2 2QQ Tel: 01223 216299 Fax: 01223 217253 Email: g.devereux@dial.pipex.com

Dr A Nicoll, PHLS Communicable Disease Surveillance Centre, London, NW9 5EQ Tel: 0181 200 6868 Email: ANicoll@phls.co.uk

Dr R Will, The National Creutzfeldt-Jakob Disease Surveillance Unit, Western General Hospital, Edinburgh, EH4 2XU Tel: 0131 332 2117

Reye syndrome

Background

Surveillance of Reye syndrome began in August 1981 as a venture shared between the (then) British Paediatric Association and the Public Health Laboratory Service Communicable Disease Surveillance Centre (CDSC). Responsibility for case ascertainment was transferred to the surveillance unit in June 1986 and from CDSC to the Department of Paediatrics at Sheffield in 1995. In the early years, the results of surveillance showed that the incidence of Reye syndrome in the British Isles was similar to that in the USA but cases occurred at a younger mean age, there was no clear seasonal (winter) peak, no striking association with influenza and chickenpox (although such cases did occur), and a higher case fatality rate.

In 1984/85 a study of risk factors mounted on to the surveillance database showed an association between Reye syndrome and consumption of aspirin. In response to this and similar findings in the USA, the Committee on Safety of Medicines issued public and professional warnings in 1986 about the use of aspirin in children under 12 years. Since then, products that contain aspirin have been required to carry warning labels.

There is increasing recognition that a number of inherited metabolic disorders - most notably those affecting fat oxidation and ureagenesis, may present as a 'Reye-like' illness, clinically and pathologically indistinguishable from Reye syndrome. The surveillance questionnaire, although currently in its simplest and shortest format since 1981, therefore seeks information on whether patients have been investigated for these disorders.

In addition to BPSU reporting, cases are also ascertained via death entries provided by the Office for National Statistics and by the Northern Ireland Statistics and Research Agency, and via laboratory reports to CDSC.

Objectives

To describe the epidemiological and clinical features of Reye syndrome in the British Isles, to monitor long term trends, and to provide a database for detailed clinical, laboratory, and aetiological studies.

Case definition

A child under 16 years old with:

- unexplained non-inflammatory encephalopathy, and *one or more of*:
- serum hepatic transaminases elevated to at least three times the upper limit of normal;
- blood ammonia elevated to at least three times the upper limit of normal;
- characteristic fatty infiltration of liver (biopsy or autopsy).

Since this definition is relatively non-specific, cases reported from surveillance year 1994/5 onwards, whose diagnosis has not been revised, have been allocated a "Reye-score"¹. Because of the non-specificity of the case definition and because there may still be "Reye-like" inherited metabolic disorders as yet undiscovered, a case of Reye syndrome can rarely, if ever, be described as confirmed; it is better designated as "compatible with" the diagnosis.

Study duration

The BPSU involvement with this study began in June 1986; it has been granted a further one year extension to July 1999.

Analysis

Between August 1981 and July 1997 a total of 604 suspected cases of Reye syndrome were reported to the surveillance unit (Table 9), but the diagnosis was subsequently revised in 151 (25%). Nearly half (48%) of the revisions were to one of the 'Reye-like' inherited metabolic disorders. In the year to July 1997, seven reports of new cases were received and further information was provided on all of them. Two of the seven diagnoses had subsequently been revised, leaving five cases whose clinical and pathological features were compatible with the case definition of Reye syndrome. All cases except two were reported via the BPSU. Two patients were ascertained via death entries alone; both had died suddenly and unexpectedly at home.

Cases compatible with a diagnosis of Reye syndrome (N=5): year to July 1997

All were males; the ages ranged between five months and 5 years with a median of 14 months. Three lived in England, and two in the Republic of Ireland. Three were ill between November and January and two in June.

Only one child survived normal, three died during their acute illness; one died four months later of a gastrointestinal haemorrhage. Two cases had had no pre-admission medications, three had been given paracetamol. All five patients had had a pre-encephalopathic viral-type prodrome - flu-like in three, gastroenteritis in two, one of whom, the five year old, also had a sore throat and high fever. In no patient was there microbiological confirmation of viral infection although one had a lymphocytic lung infiltrate at autopsy.

Four patients had been investigated for inherited metabolic disorders. The patient not investigated was the five year old. He had died suddenly and unexpectedly at home and "Reye-like syndrome" was diagnosed on the basis of cerebral oedema and microvesicular fat in the liver (and in renal tubular epithelium) identified at post-mortem.

The 'Reye Score' (possible range 1-25) ranged between 10 and 14 with a median of 12 and mean of 11.8.

Revised diagnosis cases (N = 2)

One, who survived but with neurological damage, was a nine month old male found subsequently to have medium chain acyl-CoA dehydrogenase deficiency (MCAD). The other, a previously healthy 23 month old female, was found unconscious at home and died soon after. The preliminary post-mortem findings suggested Reye syndrome, but subsequent biochemical and genetic investigations revealed MCAD.

Comment

The total reports received in 1996/97, seven, was the lowest since the surveillance scheme began in 1981. Moreover, not one of the 'non-revised' cases resembled 'classic' Reye syndrome, even though they all satisfied the basic case definition and this is reflected in their relatively low scores¹, and in their young median age, which was almost one third that of the cases reported in 1995/96 (age is not included in the score). In keeping with trends, observed in recent years, of increasing diagnostic awareness of the inherited metabolic disorders that mimic Reye syndrome, six of the seven patients were investigated for these conditions and two had the commonest fatty acid oxidation defect, MCAD. Three others had been intensively investigated by laboratories with extensive experience in these conditions but, despite the fact that two had previous histories of unexplained severe life threatening illness, and one had widespread fatty deposition in many tissues not a feature of classic Reye syndrome, no inherited metabolic disorder was found. The other patient was less comprehensively investigated. It was of concern that again, as observed among reports received in 1995/96, there was a case in whom Reye syndrome was diagnosed at autopsy, but no metabolic investigations undertaken.

In contrast to last year, no case in 1996/97 was reported to have had pre-admission aspirin, an observation consistent with the atypical clinical and epidemiological features of all the patients. The surveillance

data demonstrate, therefore, that primary prevention of 'classic' aspirin-associated Reye syndrome is continuing. Nevertheless, there is no cause for complacency because at least one such case has been reported in 1997/98 and because of the spectre of an influenza pandemic raised by the 1997 Hong Kong avian influenza outbreak, the index case of which was complicated by Reye syndrome ².

Reminders warning parents to avoid giving aspirin to children under 12 are included in the UK Departments of Health's multiphase contingency plan for pandemic influenza, but the surveillance scheme data suggest these may be too restrictive. Of the total 13 aspirin-associated cases reported since the 1986 warnings about aspirin and institution of product labelling, seven have been aged over 12 years. An analysis of the entire database going back to 1981 showed that 15/34 (44%) cases aged over 12 had reported aspirin exposure compared to 51/400 (13%) aged under 12 years. Of course surveillance data must be treated with caution as they are not as rigorous as those collected in an analytic study. Nevertheless, this observation is compatible with the hypothesis that the younger the case of "Reye", the more likely it is that the patient has one of the Reye-like inherited metabolic disorders. Detailed review of the 15 aspirin-associated cases over 12 shows that, in contrast to the 1996/97 cases, all resembled 'classic' Reye syndrome and were clinically and epidemiologically a homogeneous group with a mean Reye score of 18. Furthermore, the mean scores of cases occurring before

and after mid-1986 were similar, underlining their homogeneity. This is in contrast to reported cases as a whole, among whom the score dropped significantly after 1986¹. These surveillance scheme data have been provided, at their request, to the relevant central policy making bodies; they are of considerable public health significance and the investigators are indebted to BPSU respondents for their time and trouble in contributing to the scheme by reporting cases and providing detailed information.

Funding

The Reye syndrome surveillance scheme is funded by the National Reye's Syndrome Foundation of the UK, to whom the investigators are most grateful.

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Dr S M Hall Department of Paediatrics Sheffield Children's Hospital, Sheffield S10 2TH Tel: 0114 271 7344 Fax: 0114 755 364

Mr R Lynn BPSU, RCPC, London WIN 6DE

Tel: 0171 307 5680 Fax: 0171 307 5690 Email: r.lynn@rcpch.ac.uk

Table 9 Reye Syndrome Surveillance 1981/82 - 1996/97

Reporting period (August-July)	Total reports from the British Isles	Revised diagnosis (inherited metabolic disorder in brackets)		Cases of Reye syndrome*	Number of deaths (of cases)
1981/82	47	7	(3)	40	26
1982/83	70	10	(6)	59	34
1983/84	93	12	(3)	81	36
1984/85	64	8	(2)	56	32
1985/86	53	13	(4)	40	22
1986/87	47	21	(11)	26	13
1987/88	44	12	(3)	32	19
1988/89	31 ¹	12	(6)	18	9
1989/90	24 ¹	8	(5)	15	7
1990/91	25	12	(7)	13	5
1991/92	24 ²	6	(5)	16	6
1992/93	21 ³	10	(6)	7	4
1993/94	20 ⁴	12	(6)	3	3
1994/95	17 ⁵	3	(2)	11	3
1995/96	18 ¹	2	(1)	15	7
1996/97	7	2	(2)	5	4
TOTAL	604	151	(72)	434	230

¹ Follow-up not received for one case

² Follow-up not received for two cases

³ Follow-up not received for five cases and one case did not meet the case definition

⁴ Follow-up not received for five cases

* Compatible with the diagnosis (see text)

Subacute sclerosing panencephalitis

Background

A register of cases of subacute sclerosing panencephalitis SSPE was set up by Professor George Dick in 1970 at the request of the Joint Committee on Vaccination and Immunisation. The object was to establish the incidence of SSPE in the UK so that any change following the introduction of measles vaccination in 1968 would be recognised. In 1980 the Register was transferred to Dr Christine Miller, formerly of the Epidemiology Research Laboratory, now the PHLS Communicable Diseases Surveillance Centre (CDSC), in 1989 to Dr Norman Begg and in 1993 to Dr Elizabeth Miller.

Initially paediatricians and neurologists were asked through the medical press to notify cases to the Register; clinical and laboratory details were then requested from the clinician. From 1980 an annual letter was sent to every paediatrician and neurologist listed in the Medical Directory, asking for a slip to be returned to state whether or not a case had been seen.

SSPE was included in the BPSU reporting system from its inception in 1986 until July 1994, when it was removed from the card. In the following year, with only a passive surveillance system, no cases were brought directly to the attention of CDSC. However, two cases came to the attention of the investigators later and one case through a media report, and one through a "Yellow Card" adverse event notification to the Committee on Safety of Medicines. SSPE was returned to the BPSU card in September 1995 in order to assess whether or not the apparent decline in incidence was a true reflection of the burden of disease.

The number of cases arising since 1982 has fallen following about ten years after the decline in measles, which resulted from the introduction of vaccine (PHLS CDSC, unpublished data). However, under-reporting may also be responsible and as the incidence appears to fall the importance of complete notification increases.

Objective

To monitor the incidence of SSPE.

Methods

When a case is reported, the paediatrician is asked to provide brief clinical details on a one-page proforma. Alternatively, a request to borrow case notes is made. Analysis is initially made only on England and Wales data. If available, diagnostic specimens (serum, CSF, Fixed brain tissue) is analysed using the polymerase chain reaction and direct sequencing to detect and classify viral genome. Serum and CSF samples are also examined for evidence of intrathecal measles antibody production.

Case definition

A typical history: usually insidious onset of mental deterioration, followed (usually within a few months) by motor dysfunction, finally a progressive decerebration and ultimately death and one of the following:

- 1 raised measles antibody titres in the serum and CSF indicative of intrathecal antibody production and a higher level in the CSF compared to serum,
 - 2 typical EEG changes,
 - 3 typical brain histology or other evidence of measles virus in brain tissue,
- a definitive case requires the presence of 1 and 2.

Cases identified as SSPE should also be reported to the PIND surveillance project see page 24.

Study duration

Continuation through the BPSU is reviewed on an annual basis.

Recent results and progress

Establishing the link between SSPE and earlier measles infection relied on epidemiological analytic methods. Within the last few years it has been proposed that measles vaccination could either cause or precipitate SSPE; thus far follow-up of the 1994 MR campaign has revealed no evidence of an increase in cases. It is important that monitoring be continued in this context, so that potential delayed effects may be accounted for. Recent developments in molecular biological methods for investigation of measles virus strain variation have yielded tools for distinguishing vaccine from wild-type strains. Application of these methods will enable a definitive assessment of the nature of the causative virus, and the role, if any, of measles vaccine in the aetiology of SSPE. They will also allow determination of whether any measles virus genotypes are more strongly associated with SSPE than others. For this reason, early notification of suspect cases is now strongly encouraged, even if the diagnostic process is not yet complete, so that molecular tools may be applied to appropriate diagnostic specimens as they become available.

Six cases have been reported in the last year, two with a reported onset in 1996, and four with onset in 1997. Two cases were in Asian children, confirming the increased risk in this immigrant group. Three children had received measles vaccine at some time. In four cases there was a history of earlier measles infection. Clinical and epidemiological details from one case is still awaited. All six cases showed evidence of intrathecal production of measles antibody. Amplification of measles virus genome from a specimen of fixed brain tissue from one of the cases sent to the Central Public Health Laboratory demonstrated a wild-type strain belonging to Genotype III, unrelated to vaccine strains.

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Dr E Miller, Consultant Epidemiologist, PHLS Communicable Disease Surveillance Centre, 61, Colindale Avenue, London NW9 5EQ.
Tel: 0181 200-6868 Fax: 0181-200 7868 Email: emiller@phls.co.uk

6 New studies for 1998

Congenital brachial palsy

Background

Congenital brachial palsy (CBP) is generally thought to be due to an injury at birth to part or all of the brachial plexus, although clear evidence of injury is not present in all cases. The commonest type is Erb's palsy (see case definition). The incidence declined in the 1950s and 1960s, with an incidence in one series which reviewed cases in New York between 1932 and 1962 of 0.39 per 1000 live births¹. A recent audit at the hospital of one of the authors reported an incidence of 0.8 per 1000 (unpublished data), suggesting that the incidence may have increased in recent years. However, the true incidence in the UK is unknown.

The cause is commonly thought to be either local pressure (instruments, fingers, local soft tissue swelling, or haematoma) or lateral traction on the fetal head or upper limb causing stretching, rupture or avulsion of the brachial plexus. This results in weakness or paralysis of the arm. Associated lesions include fractures of the clavicle and proximal humerus, shoulder dislocation, phrenic nerve palsy and Horner's syndrome. Between eight and 20% of cases of Erb's palsy have been reported as to be bilateral, almost exclusively associated with breech extraction. As well as breech presentation, shoulder dystocia and large fetal weight are significant common associations, but some cases are unexplained.

The reported incidence of full muscle recovery varies widely from as little as 13% to 80% of cases. Similarly the onset of recovery is variable, ranging from two to fourteen weeks and may continue for up to 18 months. Many reported studies are of selected cases; this study will provide an opportunity to establish more accurate data about this important condition.

Severe cases with little recovery cause serious handicap - the function of the shoulder, elbow, forearm and wrist may be significantly impaired affecting social, physical and educational development. Even in less severe cases, with residual impairment of shoulder movement only, for example, significant disability can result.

The present therapeutic approach is to use physiotherapy to prevent joint contracture. Although there are reports of encouraging results using microsurgical nerve grafting techniques, the indications for surgery are unclear and controversial, and the technique remains unproven². It has been suggested that some infants who could benefit from surgery are not given the opportunity for early expert assessment and may be referred too late for surgery to be effective, it is argued that there is a "window of opportunity" between successful surgical treatment at three to six months of age. This study aims to establish the prevalence of CBP and to provide more information about the natural history of this condition.

Case definition

Surveillance: A newborn presenting with a congenital flaccid paresis of the arm (in addition thereby or may not be involvement of the hand) with a passive range of motion greater than the active.

Analytic: CBP occurs in a newborn infant who on clinical examination and observation is found to have a congenital flaccid paresis of the arm (usually one, rarely both) with a passive range of motion greater than the active. In addition, there may or may not be involvement of the hand. Cervical cord injury, or cerebral injury e.g. hypoxic ischaemic encephalopathy (H.I.E.) may coexist. X-rays may show fractures of the clavicle or humerus, a dislocated shoulder or paralysis of the hemidiaphragm.

There are three main types of lesion associated with cervical (C) root injury:-

- C5-6** The arm is adducted and internally rotated at the shoulder, the elbow is extended, the forearm pronated, and the wrist (and sometimes the fingers) flexed. This is the classical "waiter's tip" posture. (Narakas' Group I)
- C5-7** as above, although the elbow may be slightly flexed. (Narakas' Group II)
- C5-T1** the arm is totally flail with a claw hand. The arm has a marbled appearance due to vasomotor disturbance. It may (Narakas' Group IV) or may not (Narakas' Group III) be accompanied by a Horner's syndrome.

Objectives

To identify:

1. What is the incidence of C.B.P.?
2. What is the natural history of C.B.P. in the first year of life?

Study duration

March 1998 - March 1999.

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Dr G Evans-Jones, Countess of Chester Hospital, Liverpool Road, Chester CH2 1UL Tel: 01244 365059 Fax: 01244 365089

Mr S P J Kay, Consultant Plastic Surgeon, The Children's Hand Clinic & Ms A Ward, Clinical Academic Assistant, Paediatric Surgery Dept, St James's University Hospital, Beckett St, Leeds LS9 7TF Tel: 0113 2065265 Fax: 0113 2438162

Dr A Weindling, Dept of Child Health, University of Liverpool, Women's Hospital, Crown Street, Liverpool L8 7SS

Fatal/severe allergic reaction to food ingestion

Background

A number of recent studies suggest that allergic reactions to foodstuffs in children may be becoming commoner¹. However, these studies either used proxy measures, such as skin prick tests and RAST levels²; or weak methods in which case definition was imprecise, case ascertainment restricted to those referred to a clinic, or comparisons made with unreliable historical data^{3,4}.

Some reactions to food may be very severe or even fatal⁵, but there is even less evidence about the incidence of such severe reactions. Where case series are reported⁶⁻⁸ fatal allergic reaction in children under eight are extremely rare. No population based studies have been undertaken in the United Kingdom or North America. A preliminary search by the Office of National Statistics revealed only one death of a child from an allergic reaction in England and Wales in 1993 and 1994. Most paediatricians have never been involved with a case of very severe reaction and there may be a gross mismatch between the perceived risks and actual incidence of severe allergic reactions.

In spite of the absence of reliable data, prescriptions of adrenaline in the form of inhalers or auto injection devices have become more common, the assumption being that it may save lives and/or prevent severe symptoms. There is still uncertainty as to whether adrenaline is life saving⁹ but even if it is assumed that it may sometimes help, there are disadvantages with using adrenaline including:

- Potentially dangerous side effects if administered on a "if in doubt, give it" basis, such side effects may be more dangerous than possible allergic reaction¹⁰⁻¹².
- Teachers are anxious about having to decide when to administer adrenaline - may need special training, reinforced each year.
- The prescription will be required for life.
- Although relieving parental anxiety in situations in where there is considerable risk, prescribing adrenaline may create unnecessary anxiety if the risk has been exaggerated.

Inflammatory Bowel Disease in under 20 year olds

Background

While the incidence of ulcerative colitis (UC) appears static or falling, some recent reports suggest an increase in the incidence of Crohns disease (CD) in the Western world. The reason for this is uncertain but consistent with an environmental trigger. However,

Case definition

A child under 16 who has died from allergic reaction to food ingestion or an unknown allergen in the last month.

Or

A child under 16 who has been admitted to a hospital ward because of an allergic reaction to food ingestion or an unknown allergen within the last month.

Excluded

- 1 Children spending a few hours under observation without treatment in an accident and emergency department or day unit.
- 2 Children whose only symptoms of a possible allergic reaction are asthmatic and the allergen is unknown.

Objectives

- 1 To estimate the incidence of fatal and very severe allergic reactions to food in children.
- 2 To describe the circumstances in which these reactions occurred.
- 3 To describe the clinical course and management of these cases.
- 4 To determine whether such children have had previous reactions and whether the severity of previous reactions predicts later severe reactions.

Study duration

March 1998 for two years (subject to yearly review).

Method

It is assumed that all children admitted to hospital for severe allergic reactions will come under the care of a paediatrician and that these cases will be identified through the BPSU. A questionnaire with covering letter and a summary of the study protocol will be sent to reporting paediatricians.

It cannot be assumed that paediatricians will be aware of all deaths due to severe allergic reaction; particularly if the child dies at home or in an A&E department. Cases will also be identified through the Offices of National Statistics in the United Kingdom and Republic of Ireland. For the very small number of children who die (we expect one or two per year), a member of the research team may need to visit the parents for more details. This would only be undertaken if the parents have given written consent following a discussion with the reporting clinician and their family doctor.

Dr A Colver, Dr A Cant, Dr C Macdougall, Donald Court House 13 Walker Terrace, Gateshead NE8 3EB Tel: 0191 477-6000 Fax: 0191 473 0370 Email: allan.colver@ncl.ac.uk

epidemiological studies to assess environmental factors which may affect susceptible individuals are difficult because of the small numbers attending single centres. Conflicting reports on aetiology have highlighted the need for current data on disease incidence and clinical cause.

Paediatric inflammatory bowel disease (IBD) presents a number of additional clinical problems to those seen in adult disease. These include delay in diagnosis, growth failure, more aggressive course

and a higher potential for malignant change. This in part reflects the lack of specificity in presenting symptomatology and the delay in initiating effective therapy. However, many of these impressions are based on occasional reports from specialist centres. Some retrospective data related to this are available from Scotland and Wales but none from England. There have been no previous prospective studies to document clinical patterns and disease prevalence in the UK and the incidence of inflammatory bowel disease in childhood in the UK remains unknown¹.

Since a spurious increase in incidence could result from earlier diagnosis (shortening of time between symptom onset and diagnosis), it is important to have reliable data on the 16-19 year age group, some of whom may present to a paediatrician and others to an adult gastroenterologist¹. This study is therefore being carried out in collaboration with the newly formed British Society of Gastroenterology Research Unit and this collaboration, including raising the paediatric reporting age to 20 years, should ensure optimal reporting of adolescent cases.

Basic and epidemiological data from a prospective UK study on IBD is needed in order to plan appropriate care facilities, devise effective treatment strategy and direct research into this chronic disease. Furthermore in order to properly undertake future epidemiological studies on IBD, particularly to investigate environmental factors, a collection of cases will be required, the planning of which depends on good data on incidence and prevalence. This data will be obtained in the course of this study.

Study duration

June 1998-June 1999.

Case definition

Reporting Case Definition: Any individual under 20 years of age at diagnosis, and resident in the United Kingdom or Republic of Ireland who in the opinion of the notifying doctor has newly diagnosed inflammatory bowel disease (Crohn's disease, Ulcerative Colitis or indeterminate colitis), based on history, clinical, laboratory,

radiological and/or endoscopy findings. Cases will include children with isolated oral granulomatous disease and isolated peri-anal disease.

Objectives

To identify:

- 1 The annual incidence of inflammatory bowel disease (Crohn's disease, ulcerative colitis or intermediate colitis) presenting in childhood/adolescents (under 20 years of age).
- 2 The mean period between onset of first symptoms to presentation to a GP, or other doctor to diagnosis.
- 3 The site and extent of the disease process at diagnosis.
- 4 The diagnosis based on and how was the child treated.

Method

Reporting paediatricians will be sent a questionnaire to gather information on symptomatology, time between onset of symptoms, diagnosis, the method by which the diagnosis was made and the mode of management. Histology slides will be requested for one in ten reported cases and returned to the reporting physician after they have been reviewed by two independent paediatric pathologists.

It is planned to circulate all members of the British Society of Gastroenterology (BSG) using their newly developed research unit - the majority of adult gastroenterologists and gastrointestinal surgeons belong to the BSG.

Reference

Inflammatory bowel disease incidence: up, down, or unchanged?
Logan R 1998 *Gut*; 42: 309-311

Dr B Sandhu, Dr A Sawczenko, Royal Hospital for Sick Children, St Michael's Hill Bristol BS2 8BJ Tel: 0117 9285445 Fax: 0117 9285701

In collaboration with Professor R Logan, British Society for Gastroenterology Research Unit and the IBD Working Committee of the British Society of Paediatric Gastroenterology and Nutrition.

Subdural haematoma and effusion

Background

Subdural haematoma and effusion (SDH) is an important cause of death and neurological disability in childhood. Over half the cases of SDH present without evidence of skull fracture or other sign of injury to the head. Although the notion of "spontaneous origin" or arising from "minimal trauma" was claimed, an association with severe shaking injury occurring non-accidentally is now firmly established. Despite the evidence linking SDH and shaking injury, cases continue to be encountered where other non-abusive causes are

questioned within both medical and legal contexts. Rare conditions reported to be associated with subdural haemorrhage in childhood include: *H. Influenzae* and pneumococcal meningitis, haemophilia, malignancy, A-V malformation/aneurysm, post-cardiopulmonary bypass, glutaric acidemia, Allagelle's syndrome, disseminated intravascular coagulation and Menke's disease.

"Shaken baby syndrome" describes a cluster of clinical findings including retinal haemorrhages, subdural and/or subarachnoid haemorrhage, long bone metaphyseal avulsion and other skeletal injury including rib fracture and occasional vertebral injury with little or no evidence of external cranial trauma.

Difficulties in establishing the cause of SDH are more likely to be encountered in cases where there is no other evidence of trauma including those without retinal haemorrhages - estimated to be about 20 to 50% of cases. Examination of the optic fundi should ideally be undertaken by an ophthalmologist who frequently examines children using both direct and indirect ophthalmoscopy.

Case definition

Any child under two years of age with fatal and non-fatal subdural haemorrhage, haematoma or hygroma (collection of protein rich fluid in the subdural space) of any severity, arising from whatever cause and diagnosed on CT, MRI or ultrasound scan or at post-mortem examination.

Objectives

- 1 To estimate the incidence of SDH in children less than two years of age in the British Isles.
- 2 To determine the national and regional patterns of presentation and neurological/neurosurgical referral.
- 3 To assess the investigation and aetiology, and the proportion of cases where child abuse was suspected or confirmed.
- 4 To determine the factors associated with a diagnoses of non-accidental shaking injury.
- 5 To establish the short term outcome at follow-up.

Study duration

April 1998-April 1999

Methods

Following a report to the BPSU office respondents are asked to complete a questionnaire. All data requested will be anonymised with initials, date of birth as the identifiers.

Fatal cases will also be reported by the Office of National Statistics reporting scheme and approaches made to the coroner involved for information. A questionnaire will be sent to the pathologist who completed the post-mortem examination.

Reference

Committee on Child Abuse and Neglect, American Academy of Pediatrics. Shaken baby syndrome: inflicted cerebral trauma. *Pediatrics* 1993; 92:872-5

*Dr CHobbs, Community Paediatrics, St James' University Hospital, Leeds LS9 7TF
Tel: 0113 2064327 Fax: 0113 2064877 Email: cjhobbs@netcomuk.co.uk
Dr J Wynne, Dr J Livingston, Leeds General Infirmary, Belmont House, 3/
5 Belmont Grove Leeds LS2 9NP Tel: 0113 2926106
Dr AM Childs, Dr A Seal, Leeds, General Infirmary Clarendon Wing, Leeds LS2
Tel: 0113 2432799*

7 The international perspective

Historical background

The origins of the first national paediatric surveillance unit, the BPSU, can be traced back to 1979-83. The British Paediatric Association and the Public Health Laboratory Service at that time was relatively unsuccessful in undertaking passive surveillance of conditions such as necrotising enterocolitis, Reye syndrome and Kawasaki disease. Paediatricians often failed to remember to report cases of rare conditions when they were diagnosed. This led to the development of active surveillance, sending paediatricians monthly reminders of the conditions they were being asked to report which is the basis of the system that evolved. The BPSU began formally in 1986 and has been continuously in action, with the aims of:-

- Facilitating research into uncommon paediatric infections, disorders or injuries of public health importance for the advancement of knowledge and improvement of prevention, treatment and service planning.
- Lessening the burden on doctors of requests for reporting.
- Increasing the awareness of the less common disorders of childhood.
- Responding rapidly to public health emergencies.

Recent developments

Following the success of the BPSU the same methodology was adopted, and adapted in the 1990s to other countries whose paediatric services are amenable to an active surveillance approach. In 1996/7 there were nine other paediatric surveillance units including Canada using 'active' surveillance system approach to monitor rare disorders in a total child population (aged under sixteen years) of over 45 million.

A number of units have come to be studying the same or related conditions (page 36). These approaches have not necessarily been co-ordinated or exploited to their full potential. The units are now attempting to encourage their respective national researchers looking at the same conditions to share and standardise protocols, case definitions and study periods, to pool data etc. This is not easy to achieve but it is hoped to facilitate this by establishing an 'International Network of Paediatric Surveillance Units' in 1998.

Australian Paediatric Surveillance Unit (APSU)

The APSU became active in May 1993. It currently circulates details to between 900 and 1000 clinicians covering a child population of 3.9 million. The overall response rate is over 90% but has varied substantially between sub-specialities from 79% to 100%. Rates have been lower for non-paediatric specialists recruited to report particular conditions. An annual report is produced and in 1994, 25% of clinicians reported one

case, 5% reported 2-4 cases, and less than 1% reported more than five cases while 69% of clinicians did not encounter a case of the conditions under surveillance.

Twelve conditions, including a number of infectious and vaccine-preventable diseases were surveyed in 1997. These were acute flaccid paralysis, arthrogryphosis multiplex congenita, congenital adrenal hyperplasia, congenital rubella, congenital and neonatal varicella, haemorrhagic disease of the new-born, neonatal herpes simplex virus infection, HIV/AIDS, Hirschsprung's disease, Kawasaki disease, primary immunodeficiency disorders (including severe combined immunodeficiency) and subacute sclerosing panencephalitis. Studies of childhood dementia, Kawasaki disease and Rett syndrome have already been completed.

The APSU has provided data to the National Health and Medical Research Council of Australia, the World Health Organisation, the International Committee for Vitamin K deficiency Surveillance and the Commonwealth and State Health Departments. It has received considerable attention from the national media and the medical press, through which it has informed both the general public and the wider medical community.

Contacts

Dr Elizabeth Elliott, Dr Katrina Williams, PO Box 3315, Parramatta, NSW 2124 Australia Tel: + + 61 29845 3000/3005 Fax: + + 61 29845 3082 Email: apsu@nch.edu.au

Canadian Paediatric Surveillance Programme (CPSP)

Set up in 1996, the Canadian Paediatric Surveillance Programme (CPSP) is now into its second year. The CPSP represents an alliance of the Canadian Paediatric Society, and the Laboratory Centre for Disease Control, (the Canadian equivalent of the PHLS in England and Wales), along with involvement from the First Nation (aboriginal) and provincial public health bodies. Currently over 2,000 clinicians covering a child population of 6 million are circulated with a monthly mailing card. Response rates have increased rapidly and are now around 90%. Studies currently on-going include acute flaccid paralysis, SSPE, congenital rubella, sporadic CJD, haemorrhagic disease of the newborn.

Contacts

Dr Victor Marchessault, Canadian Paediatric Surveillance Programme, Canadian Paediatric Society, 100-2204 Walkley Road, Ottawa ON K1G 4A8, Canada Tel: + + 613 526 9397 Fax: + + 613 526 3332 Email: cpsp@cps.ca
Dr Paul Sackett, Bureau of Infectious Diseases, Laboratory Centre for Disease Control, Ottawa, Ontario, K1A 0L2 Tel: + + 613 941 1288 Fax: + + 613 998 6413 Email: psackett@isldcp3.lmc.ca

German Paediatric Surveillance Unit (ESPED)

Encouraged by the success of the BPSU, a German adaptation of the surveillance scheme called the ESPED was initiated in July 1992 to cover the country which has one of the largest child populations of any of the units (around 12 million). The surveillance system differs from the original British methodology in that cards are sent to paediatric department heads to complete. The response rates for the 500 groups of clinicians have risen significantly from 75% in 1992 to 93% in 1997, with the follow-up rate of completion of questionnaires at around 90%.

A number of studies have been completed. These include Reye syndrome, Ondine's curse (primary failure of respiratory regulation), Kawasaki disease, acute renal failure and acute liver failure. In 1997 the conditions under surveillance were: fatal and near fatal asthma, invasive infection with *Haemophilus influenzae* type b, insulin dependent diabetes mellitus in under fives, neonatal thrombosis, acute renal failure, auto-immune hepatitis, multiple sclerosis, systemic pneumococcal infection, haemorrhagic disease of the newborn, severe pertussis and varicella complications. In 1998 it is planned to add surveillance for severe neonatal infections due to fungi (candida), septic meningitis following MMR vaccination, and haemolytic uraemic syndrome.

Contacts

Professor R Von Kries, Institute für Social Paediatric und Jugendmedizin der Ludwig-Maximilians Universität München, Germany

Tel: ++89 71009 314 Fax: ++89 71005 315

Email: esped@rz.uni-dusseldorf.de

Professor E Schmidt, Universitäts-Kinderklinik, Moorenstrasse 5, 4000 Dusseldorf 1, Germany

Latvian Paediatric Surveillance Unit

This Latvian paediatric surveillance system began in 1997. Though currently not using a card mailing system all rare disease are reported to the Children's Hospital in Riga. In 1997 there have been two cases of congenital hypothyroidism, one nesidioblastosis, salt losing congenital adrenal hyperplasia, 38 primary diabetes (type 1), 17 cases of leukaemia (myeloleucosis - three), 16 cases of coeliac disease (primary diagnosed) in the age group one to 16 years and one Reye syndrome.

Contact

Professor E Bikis, Children's Hospital, 45 Viembasgāte, LT-1004, Riga, Latvia

Tel: ++371 760571 Fax: ++371 7621568 Email: aspedlat@com.latnet.lv

Malaysian Paediatric Surveillance Unit (MPSU)

The MPSU was established in December 1993 and surveillance began in September 1994 under the auspices of the Malaysian Paediatric Association. It covers all of Malaysia with a child population of between seven and eight million. The Unit has adopted the classical BPSU methodology with cards being circulated to around 340 paediatricians and surgeons. The initial response rate is encouraging at 75%, having risen as the system becomes more familiar to respondents. Only 13% of respondents have never returned a card. Initially four conditions are under surveillance, paediatric HIV and AIDS, neonatal meningitis, acute fulminant liver failure and death from asthma. 1997 has been particularly difficult for the MPSU because of the effects of economic difficulties affecting South East Asia however the surveillance for Duchenne muscular dystrophy has now commenced.

Contact

Dr Jacqueline Ho, Dr HSS Amar, Department of Paediatrics, Hospital Ipoh, 30990 Ipoh, Malaysia

Tel: ++605 253 333 Fax: ++605 253 1541 Email: jho@pc.jaring.my

Netherlands Paediatric Surveillance Unit (NSCK)

The Dutch Unit started surveillance in October 1992. Over 300 paediatricians in 152 general hospitals receive the monthly card. The child population is 2.8 million. As in Germany, the reporting methodology has been modified to suit local organisation of care. The eight university hospitals have each nominated specific personnel to respond for separate disorders and to be responsible for reporting all cases in that hospital. The overall response rate has risen from 83% in 1992 to over 90% in 1997. The follow-up rate is also high at over 93%. The importance of full case ascertainment has been realised and where possible alternative complementary data sources have been recruited for particular disorders. For example, surveillance of diabetes was strengthened by the inclusion of the Dutch Diabetic Association, while surveillance of invasive *Haemophilus influenzae* infection was improved by using reports from the Netherlands Reference Laboratory for bacterial meningitis.

Thirteen studies are either underway or have been completed: acute flaccid paralysis*, coeliac disease*, insulin dependent diabetes mellitus*, group B streptococcal infections*, invasive *Haemophilus influenzae* infection, haemolytic disease of the newborn (non ABO non RhD), haemorrhagic disease of the newborn, HIV/AIDS*, neural tube defects*, post-neonatal mortality in premature and dysmature born children* sickle cell disease and thalassemia major and venous thromboembolic complications.

** under surveillance in 1997.*

Contact

*Professor S.P. Vanloove-Vanhorick, Dr. R.A. Hirsing, NPG-TNO Postbus 124, 2300 AC Leiden, Netherlands
Tel: ++ 31 71 518 18 16 Fax: ++ 31 71 518 18 18 Email: hirsing@pg.tno.nl*

New Zealand Paediatric Surveillance Unit (NZPSU)

This is the newest surveillance unit and only began in 1997 with financial support from the Ministry for Health and advice from the Australian Paediatric Surveillance Unit. Covering a child population of 0.8 million each month 163 clinicians are circulated with a surveillance card. The response rate is already excellent running at 96%. Six studies are currently being surveyed these are acute flaccid paralysis, HIV, hemolytic uraemic syndrome, vitamin K deficiency bleeding, congenital rubella and herpes simplex virus.

Contact

*Professor B Taylor, Dr N Dickson, Ms N Dow, University of Otago, Dept of Paediatrics and Child Health, Dunedin School of Medicine, PO Box 913, Dunedin New Zealand
Tel: 03 474 7825 Fax: 03 474 7817 Email: nzpsur@gandolf.otago.ac.nz*

Papua New Guinea Surveillance Unit (PGNSU)

This unit began in 1996 and is closely associated with the Paediatric Association of PNG. Covering a national child population of 1.8 million there are currently 34 doctors on the mailing list though this is expected to increase to about 40 by the end of 1998. Response rate for the past six months is around 71.3% and this is expected to increase. Since 1996 surveillance has been undertaken for nine conditions, acute flaccid paralysis (17 reports); insulin dependent diabetes mellitus (4 reports); congenital adrenal hyperplasia (13 reports); neurologic endemic cretinism (3 reports) renal tubular acidosis (19 reports); sub-acute sclerosing panencephalitis (58 reports); thalassaemia (57 reports) and HIV/AIDS (24 reports). In 1998 these may be joined by nephrotic syndrome.

Contact

*Dr Graham Ogle Co-ordinator PNG Paediatric Surveillance Unit, PO Box 3478, Boroko, NCD, Papua New Guinea
Tel: ++675 325 6901 Fax: ++675 323 0419 Email: hopepng@datec.com.pg*

Switzerland Paediatric Surveillance Unit (SPSU)

The SPSU was established in early 1995 under the auspices of the Swiss Paediatric Association and the Federal Office of Public Health. The German Unit provided the software to run the system and is currently advising the SPSU. Report cards are circulated to hospital or clinic-based paediatricians (i.e. not to those delivering primary care). There are approximately 500 respondents in 41 clinics, covering a total child population of 1.3 million children. The most recent response rate was 98%. The six conditions under surveillance in 1997 were: acute flaccid paralysis, congenital rubella syndrome, congenital toxoplasmosis, haemolytic uraemic syndrome, periventricular leucomalacia and haemorrhagic disease of the newborn. It is planned to add surveillance for complications of streptococcal disease and inflammatory bowel disease in 1998.

Contact

*Dr. H.P. Zimmerman, Swiss Paediatric Surveillance Unit, Hess-Strasse 27e, 3097 Bern-Leibefeld, Switzerland Tel: ++4131 323 8710
Fax: ++4131 323 8795 Email: hans-peter.zimmermann@bag.admin.ch*

Table 10 National Paediatric Surveillance Units - Conditions under surveillance 1997

Australia APSU	acute flaccid paralysis arthrogryposis multiplex congenita congenital adrenal hyperplasia congenital/neonatal varicella congenital rubella HDN (vitamin K deficiency bleeding) Hirschsprung's disease HIV/AIDS Kawasaki disease neonatal herpes simplex primary immunodeficiency disorders SSPE	Netherlands NSCK	acute flaccid paralysis coeliac disease congenital adrenal hyperplasia diabetes mellitus HIV/AIDS invasive haemophilus influenzae neural tube defects group B streptococcal infections pertussis rota virus admission venous thromboembolic complications
Canada CPSP	acute flaccid paralysis congenital rubella Creutzfeldt-Jacob disease haemorrhagic disease of the newborn neural tube defects SSPE	New Zealand NZPSU	acute flaccid paralysis haemolytic uraemic syndrome HIV/AIDS herpes simplex virus congenital rubella vitamin K deficiency bleeding
Germany ESPED	autoimmune hepatitis fatal and near fatal asthma haemorrhagic shock encephalopathy syndrome idiopathic thrombocytopenia insulin dependent diabetes (age <5y) multiple sclerosis pertussis stroke (through thrombosis of cerebral vessels) systemic pneumococcal infection vitamin K deficiency bleeding	Papua New Guinea PNGSU	acute flaccid paralysis IDDM congenital adrenal hyperplasia congenital hypothyroidism HIV/AIDS neurologic endemic cretinism renal tube acidosis SSPE thalassaemia
Latvia	adrenoleukodystrophy aplastic anaemia coeliac disease diabetes nesidioblastosis leukaemia	Swiss SPSU	acute flaccid paralysis congenital rubella congenital toxoplasmosis haemolytic uraemic syndrome periventricular leucomalacia vitamin K deficiency bleeding
Malaysia MPSU	death from asthma HIV/AIDS neonatal meningitis	UK & Eire BPSU	cerebral oedema following diabetic ketoacidosis congenital rubella haemolytic uraemic syndrome hepatitis C infection HIV/AIDS haemophilus influenzae infection neonatal meningitis pyridoxine dependent seizures Reye syndrome SSPE

Appendix A

Completed studies prior to 1997

By mid 1997 the British Paediatric Surveillance Unit had completed thirty-two studies. Information about these studies has been included in previous annual reports of the BPSU, which are

available from the BPSU office. The studies and their principal investigators are listed below. For addresses see the list at the end of this report.

1. **X-linked anhydrotic ectodermal dysplasia**
(June 1986 – August 1986)
Dr A Clarke
2. **Lowe syndrome**
(June 1986 – February 1988)
Dr C McKeown
3. **Insulin dependent diabetes in under 15s**
(January 1988 – December 1988)
Professor J D Baum
4. **Drowning and near drowning**
(January 1988 – December 1989)
Professor J Sibert
5. **Higher order births**
(January 1989 – December 1989)
Professor M Levene
6. **Haemorrhagic disease of the newborn**
(March 1988 – February 1990)
Dr A W McNinch, Dr H Tripp
7. **Haemorrhagic shock encephalopathy syndrome**
(June 1986 – December 1988)
Dr S Hall
8. **Haemolytic uraemic syndrome**
(June 1986 – December 1989)
Dr S Hall
9. **Neonatal herpes**
(June 1986 – Dec 1991)
Ms P A Tookey, Professor C S Peckham, Dr R Dinwiddie
10. **Kawasaki disease**
(June 1986 – December 1992)
Dr S Hall
11. **Galactosaemia**
(January 1988 – September 1991)
Mrs A Green, Dr J Holton, Dr M Honeyman, Professor J Leonard
12. **Congenital toxoplasmosis**
(June 1989 – May 1990)
Dr S Hall
13. **Acute rheumatic fever**
(January 1990 – December 1990)
Dr C Boyd-Scobie, Dr S Hall
14. **Rett syndrome**
(April 1990 – June 1990)
Dr A Kerr
15. **Measles, mumps, rubella/meningococcal meningitis**
(January 1990 – December 1991)
Dr N Begg
16. **Chemistry set poisoning**
(January 1991 – April 1992)
Dr E Mucklow
17. **Androgen insensitivity syndrome**
(September 1991 – August 1993)
Professor I A Hughes
18. **Acute flaccid paralysis**
(July 1991 – June 1994)
Dr N Begg
19. **Long term parenteral nutrition**
(February 1992 – April 1992)
Professor D Candy, Professor E Ross, Dr S Devane
20. **Insulin dependent diabetes**
(January 1992 – December 1992)
Professor J D Baum, Ms E Wadsworth
21. **Juvenile dermatomyositis**
(June 1992 – December 1993)
Dr D Symmons, Dr A Sills
22. **Congenital dislocation of the hip**
(April 1993 – July 1993)
Dr C Dezateux, Dr S Godward
23. **Haemophagocytic lymphohistiocytosis**
(September 1991 – August 1994)
Professor S Strobel, Dr J Pritchard, Dr M Leyton
24. **Non-accidental poisoning/Munchausen Syndrome by proxy**
(September 1992 – August 1994)
Dr P Davis, Professor J Sibert, Professor S R Meadow
25. **Neonatal necrotising enterocolitis**
(October 1993 – October 1994)
Professor A Lucas, Ms R Abbott
26. **Vitamin K deficiency bleeding**
(January 1993 – December 1994)
Dr A McNinch, Dr J Tripp
27. **Biliary atresia**
(March 1993 – February 1995)
Dr J P McKiernan, Dr D Kelly
28. **Congenital syphilis**
(July 1993 – July 1996)
Dr T Lissauer, Dr A Nicoll
29. **Medium chain acyl-CoA dehydrogenase**
(March 1994 – March 1996)
Dr J Pollitt, Professor J V Leonard
30. **Transient and permanent neonatal diabetes**
(July 1994 – August 1995)
Dr J Shield, Professor J D Baum
31. **Adverse neonatal outcomes of delivery or labour in water**
(April 1994 – April 1996)
Ms P Tookey, Dr R Gilbert
32. **Congenital cataract**
(October 1995 – October 1996)
Ms J Rahi

Appendix B Published papers

- Vaccine failures after primary immunisation with Haemophilus influenza type-b conjugate vaccine without booster: Booy R, Heath PT, Slack MPE, Begg N, Moxon ER. *Lancet* 1997; 349: 1197-202
- The epidemiology of rubella in England and Wales before and after the 1994 measles and rubella vaccination campaign: 4th joint report from the PHLS & the National Congenital Rubella Surveillance Programme. Miller E, Waigh PA. *CDR Review* 1997; 7: No2 R26-R32
- Neonatal herpes simplex virus infection in the British Isles: Tookey P, Peckham CS. *Paediatric and Perinatal Epidemiology* 1997; 10: 432-442
- Aetiopathology and genetic basis of neonatal diabetes: Shield JPH, Gardner RJ, Wadsworth EJK, et al. *Arch. Dis. Child.* 1997; 76: F39-F42
- Chemistry Set Poisoning: Mucklow E S. *Internat. Journ. Clin. Pract.* 1997; 51.5: 321-23
- AIDS and HIV infection (data to end of January 1997): Molesworth A, Tookey P. *CDR Review* 1997; 7(9): R132-34
- Uptake of interventions to reduce mother-to-child transmission of HIV in the United Kingdom and Ireland: Gibb DM, MacDonagh SE, Tookey PA, Duong T, Nicoll A, Goldberg DJ, Hudson CN, Peckham C. *AIDS* 1997; 11: F53-F58
- Malignancies in UK children with HIV infection acquired from mother to child transmission. Evans JA, Gibb DM, Holland FJ, Tookey PA, Pritchard J, Ades AE. *Arch. Dis. Child.* 1997; 76:330-33
- Polio Eradication: Surveillance Implications for the United Kingdom: Salisbury DM, Ramsay ME, White JM, Brown DW. *The Journ. of Infect. Dis.* 1997; 175 (Suppl 1): S156-9
- Neonatal screening for inborn errors of metabolism: cost, yield and outcome: Pollitt R J, Green A, McCabe CJ, et al. *Health Technology Assessment Report* 1997; 1:1-202
- Dermatoglyphics, fetal growth and insulin dependent diabetes in children under five: Shield JPH, Wadsworth E, Baum JD. *Arch. Dis. Child.* 1997 72(2): 159-160,
- A case-control study of environmental factors associated with diabetes in the under 5s. Wadsworth EJ, Shield JP, Hunt LP, Baum JD. *Diabetic Medicine.* 1997; 14(5):390-6
- Screening for congenital dislocation of the hip in the newborn and young infants: Dezateux C, Godward S. *Edinburgh* 1997; Churchill Livingstone.
- The British Paediatric Surveillance Unit - a pioneering method for investigating the less : common disorders of childhood. Report of a seminar held in June 1995: Hall SM, Nicoll A. *Child: Care, Health and Development* 1998; 24: 2:129-143
- Epidemiology and detection of HIV-1 among pregnant women in the United Kingdom: results from national surveillance 1988-96: Nicoll A, McGarrigle C, Brady, AR, Tookey P, et al. *BMJ* 1998; 316: 253-258
- Factors affecting uptake of antenatal HIV testing in London: results of a multicentre study. Gibb DM, MacDonagh SE, Ramyani G, Tookey P, Peckham CS, Ades AE. *BMJ* 1998; 316: 259-61
- Procedures, placement, and risks of further abuse after Munchausen syndrome by proxy, non-accidental poisoning, and non-accidental suffocation: Davis P, McClure RJ, Rolfe K, Chessman N, Pearson S, Sibert JR, Meadow R. *Arch. Dis. Child.* 1998; 78: 217-221
- Prospective surveillance study of medium chain acyl-CoA dehydrogenase deficiency in the UK: Pollitt RJ, Leonard JV. *Arch. Dis. Child.* 1998; 79: 116-119

Appendix C Recent presentations

1st RCPCH Annual Scientific Meeting 1997

Recent outcome of biliary atresia in the British Isles.
McKiernan P.

Aspirin and Reye's syndrome: a possible biochemical relationship.
Moore R.

Abstracts & conferences

Management of HIV-infected pregnant women in the UK. Research
in Midwifery Conference, Aston University, 8 April 1997.
Tookey P.

2nd RCPCH Annual Scientific Meeting 1998

Patterns of Presentation of Children with Congenital/Infantile
Cataract in Britain.

Rahi JS, British Congenital Cataract Interest Group.

National Surveillance of Paediatric Hepatitis C.
Neave PE, Tookey PA, Gibb DM

Pyridoxine dependent Seizures in the UK: the BPSU Study.
Baxter P

Malignancies occurring in children with vertically acquired HIV
infection in the UK.

Evans JA, Holland, FJ; Tynan, DG; Novelli, V; Sharland, M; Berry,
T; Tookey, PA; Gibb, DM

Appendix D Contacts and information

Anaphylaxis

The Anaphylaxis Campaign, PO Box 149, Fleet GU13.

Congenital Rubella

SENSE (Deaf/Blind Rubella Handicaps) 31 Grays Inn Road, London WC1X 8PT.

Crohn's Disease and Ulcerative Colitis

Mrs Margaret Lee, Crohn's in Childhood Research Association, Parkgate House, 356 West Barnes Lane, Motpur Park, New Maiden KT3 6NB.

Encephalitis Effects

Encephalitis Support Group, Pasture House, Normanby, Sinnington, York YO6 6RH.

Erb's Palsy

Erb's Palsy Support Group, 2 Willoughby Close, Coventry CV3 2GS.

Haemolytic Uraemic Syndrome

HUSH, PO Box 1303, Sheffield S6 6LY

HIV/AIDS

Barnardos Positive Orphans, Unit 22, Angel Gate, City Road, London EC1V 2PT.

Positively Women, 347-349 City Road, London EC1V 1LR.

Meningitis

National Meningitis Trust, Fern House, Bath Road, Stroud, Gloucestershire.

Meningitis Research Foundation, 13 High Street, Thornbury, Bristol BS35 2BS

Reye Syndrome

Reye's Syndrome Foundation of the UK, Mrs G Denney 15 Nicholas Gardens, Pyrford, Woking, Surrey GU22 8SD.

For information on a variety of
rare childhood disorders
a directory of support groups and their
addresses has been produced by:

'Contact a Family'

170 Tottenham Court Road,
London W1P 0HA.

Health.fudo.gov

*http://rare.diseases.
info.nih.gov*

Useful web-site addresses

Royal College of Paediatrics and Child Health

<http://www.rcpch.ac.uk>

Contact a Family (CaF)

<http://www.cafamily.org.uk>

Paediatric Aids Resource Centre

<http://www.ed.ac.uk/~clah/parc.html>

Organising Medical Networked Information

<http://omni.ac.uk/>

Communicable Disease Surveillance Centre of the Public Health Laboratory Service

<http://www.open.gov.uk/cdsc/>

Office of National Statistics

<http://www.emap.com/ons97/>

On-Line Mendelian Inheritance in Man (OMIM)

<http://www3.ncbi.nlm.nih.gov/Omim/>

National Organization for Rare Disorders (NORD)

<http://www.NORD-rdb.com/~orphan>

-or-

<http://www.pcnet.com/~orphan>

Unknown and Rare Disorders

<http://www.dubuque.net/~nancmann/>

*www.rare.diseases.
org*

*Rare Orphan Clinical
Research Database*

*http://rare.diseases.info.nih.gov/orf/
www.prot/1dore.shtm*

Further useful web-sites are available from the
**Guide to the Internet Sites in the Area of
Paediatrics and Child Health**
produced by the RCPCH.

*Ped info.
www.pedinfo.org*

Appendix E Contact addresses

Dr G K Adak, Central Public Health Laboratory, 61 Colindale Avenue, London NW9 5HT

Dr R Bartlett, Director, PHLS, Communicable Disease Surveillance Centre, 61 Colindale Avenue, London NW9 5EQ

Professor J D Baum, Institute of Child Health, Royal Hospital for Sick Children, St Michael's Hill, Bristol BS2 8BJ

Dr P Baxter, Consultant Paediatric Neurologist, Ryegate Children's Centre, Sheffield Children's Hospital, Sheffield S10 2TH

Dr N Begg, PHLS Communicable Disease Surveillance Centre, 61 Colindale Avenue, London NW9 5EQ

Dr E Bikis, Children's Hospital, 45 Viembasgarve, LY-1004, Riga, Latvia

British Society of Gastroenterology, 3 St Andrews Place, Regent's Park, London NW1

Professor D Candy, Department of Child Health and Community Paediatrics, King's College School of Medicine and Dentistry, London SW5

Dr A Cant, Royal Victoria Infirmary, Queen Victoria Road, Newcastle upon Tyne NE1 4LP

Dr A Clarke, University of Wales, Heath Park, Cardiff CF4 4XW

Professor R Cooke, Institute of Child Health, Liverpool Children's Hospital, Eaton Road, Liverpool L12 2AP

Dr P Davis, Department of Community Child Health, Lansdowne Hospital, Sanatorium Road, Cardiff CF1 8UL

Dr S Devane, Department of Child Health and Community Paediatrics, King's College School of Medicine and Dentistry, London SE5

Ms G Devereux, Paediatric Administration Office, Box 45, Addenbrooke's NHS Trust, Hills Road, Cambridge CM2 2QQ

Dr C Dezateux, Department of Epidemiology, Institute of Child Health, 30 Guilford Street, London WC1N 1EH

Dr R Dhillon, Department of Cardiology, Hospital for Sick Children, Great Ormond Street, London WC1

Dr R Dinwiddie, Institute of Child Health, 30 Guilford Street, London WC1N 1EH

Dr D Dunger, Department of Paediatrics, John Radcliffe Hospital, Headington, Oxford OX3 9DU

Dr J Edge, Department of Paediatrics, John Radcliffe Hospital, Headington, Oxford OX3 9DU

Dr E Elliott, Australian Paediatric Surveillance Unit, PO Box 3315, Parramatta, NSW 2124 Australia

Dr E G Evans-Jones, Countess of Chester Hospital, Liverpool Road, Chester, CH2 1UL

Faculty of Paediatrics of the Royal College of Physicians of Ireland, 6 Kildare Street, Dublin 2, Republic of Ireland.

Dr J Fogarty, Department of Public Health Medicine, Merlin Park Hospital, Galway, Republic of Ireland

Dr D Goldberg, Scottish Centre for Infectious & Environmental Health Ruchill Hospital, Glasgow G20 9NB

Professor P Goodfellow, Department of Genetics, University of Cambridge School Medicine, Addenbrookes Hospital, Cambridge CB2 2QQ

Mrs A Green, The Child and Family Centre, 142 Maas Road, Northfield, Birmingham B31 2PR

Dr M Guy, Consultant in Public Health Medicine, Brent and Harrow Health Authority, Crace House, Harrobian Business Village, Bessborough Road, Harrow HA1 3EX

Dr S Hall, c/o Storrs House Farm, Storrs Lane, Sheffield, South Yorkshire S6 6GY

Dr M Hawkins, Department of Paediatrics, John Radcliffe Hospital, Headington, Oxford OX3 9DU

Dr P Heath, National Haemophilus Reference Laboratory, John Radcliffe Hospital, Oxford OX3 9DU

Dr C Hobbs, St James's Children's Hospital, Beckett Street, Leeds, West Yorkshire LS9 7TF

Dr J Ho, MPA Secretariat, Institut Pedatrik, Hospita Kuala Lumpur, 5074 Kuala Lumpur, Malaysia

Dr D Holt, Karim Centre for Meningitis Research, Queen Charlotte's & Chelsea Hospital, Goldhawk Road, London W6 0XG

Professor J B Holton, Department of Child Health, Royal Hospital for Sick Children, St Michael's Hill, Bristol BS2 8BJ

Dr M Honeyman, The Child and Family Centre, 142 Maas Road, Northfield, Birmingham B31 2PR

Professor I A Hughes, University of Cambridge School of Clinical Medicine, Addenbrooke's Hospital, Cambridge CB2 2QQ

Dr I Jones, Scottish Centre for Infection & Environmental Health, Ruchill Hospital, Glasgow G20 9NB

Dr A M Kemp, Community Child Health, Community Health Headquarters, Lansdowne Hospital, Cardiff CF1 8UL

Dr A Kerr, Quarrier's Homes, Bridge of Weir, Renfrewshire PA1 3SA

Dr G Laing, Consultant Community Paediatrician, Child Health Unit, St Leonard's Hospital, Nutaal Street, London N1 5LZ

Dr M Layton, Department of Haematological Medicine, King's College Hospital, Denmark Hill, London SE5 8RX

Professor J V Leonard, Medical Unit, Institute of Child Health, 30 Guilford Street, London WC1N 1EH

Professor M Levene, Leeds General Infirmary, Belmont Grove, Leeds LS2 9NS

Dr I A F Lister Cheese, Department of Health, Wellington House, 133-155 Waterloo Road, London SE1 8EU

Dr T Lissauer, Department of Child Health, St Mary's Hospital, London W2 1NY

Professor A Lucas, Infant and Child Nutrition Unit, Institute of Child Health, 30 Guilford Street, London WC1 1EH

- R Lynn, Scientific Coordinator, British Paediatric Surveillance Unit, Royal College of Paediatrics and Child Health, 50 Hallam Street London W1N 6DE
- Professor V Marssault, Canadian Paediatric Surveillance Programme, Canadian Paediatric Society, 100-2204 Walkley Road, Ottawa ON K1G 4A8, Canada
- Dr R MacFaul, Paediatric & Child Health Services, Room 514 NHSE HQ, Dept of Health, Wellington House, 133-155 Waterloo Road, London SE1 8NG
- Dr C McKeown, Department of Medical Genetics, St Mary's Hospital, Manchester M13 0JH
- Dr A McNinch, Department of Child Health, Postgraduate Medical School, Royal Devon & Exeter Hospital, Barrack Road, Exeter EX2 5DW
- Professor S R Meadow, Department of Paediatrics and Child Health, St James's University Hospital, Leeds LS9 7TF
- Dr D V Milford, Birmingham Children's Hospital NHS Trust, Laboratory of Enteric Pathogens, Ladywood Middleway, Birmingham B16 8ET
- Dr E Miller, PHLS Communicable Disease Surveillance Centre, 61 Colindale Avenue, London NW9 5EQ
- Dr A M Mott, Royal Hospital for Sick Children, St Michael's Hill, Bristol BS2 8BJ
- Professor R Moxon, National Haemophilus Reference Laboratory, John Radcliffe Hospital, Oxford OX3 9DU
- Dr E Mucklow, Keep Cottage, 5 Castle Lane, Carisbrooke, Isle of Wight PO30 1PH
- Dr A Nicoll, PHLS, Communicable Disease Surveillance Centre, 61 Colindale Avenue, London NW9 5EQ
- Dr S O'Brien, PHLS Communicable Disease Surveillance Centre, 61 Colindale Avenue, London NW9 5EQ
- Office of National Statistics, St Catherine's House, Kingsway, London WC2 6JP
- Dr G Ogle, PNGSU, PO Box 3478, Boroko, NCD, Papua New Guinea.
- Professor C S Peckham, Department of Paediatric Epidemiology & Public Health, Institute of Child Health, 30 Guilford Street, London WC1 1EH
- Professor T H Pennington, Department of Medical Communicable Disease Microbiology, Aberdeen Royal Hospital, Forester Hill, Aberdeen AB9 2ZB
- Dr R Pollitt, Neonatal Screening Laboratory, Children's Hospital, Sheffield S10 2TH
- Dr J Pollock, Royal College of Paediatrics and Child Health, 50 Hallam Street London W1N 6DE
- Dr J Rahi, c/o Dept of Epidemiology & Public Health, Institute of Child Health, 30 Guilford Street, London WC1N 1EH
- Dr M Ramsay, PHLS Communicable Disease Surveillance Centre, 61 Colindale Avenue, London NW9 5EQ
- Professor C Roberts, Deputy Director, Public Health Laboratory Service, Headquarters, 61 Colindale Avenue, London NW9 5EQ
- Professor E M Ross, King's College, South Western Hospital, Pultross Road, London SW9 9NU
- Dr B Rowe, Central Public Health Laboratory, 61 Colindale Avenue, London NW9 5HT
- Royal College of Obstetricians and Gynaecologists, 27 Sussex Place, Regent's Park, London NW1 4RG
- Royal College of Paediatrics and Child Health, 50 Hallam Street London W1N 6DE
- Royal College of Pathologists, 2 Carlton House Terrace, London SW1Y 5AF
- Royal College of Physicians (Ireland), Faculty of Paediatrics, 6 Kildare Street, Dublin 2
- Dr B Sandhu, Institute of Child Health, Bristol Childrens Hospital, St Michaels Hill BS2
- Professor E Schmidt, Universitäts-Kinderklinik, Moorenstrasse 5, 4000 Dusseldorf 1, Germany
- Professor J R Sibert, Dept of Child Health, University of Wales College of Medicine, Llandough Hospital, Penarth, South Glamorgan CF64
- Dr A J Sills, Royal Liverpool Children's Hospital NHS Trust, Alder Hey, Eaton Road, Liverpool L12 2AP
- Dr P Sockett, Bureau of Infectious Diseases, Laboratory Centre for Disease Control, Ottawa, Ontario, K1A 0L2
- Dr M Slack, National Haemophilus Reference Laboratory, John Radcliffe Hospital, Oxford OX3 9DU
- Professor S Strobel, Institute of Child Health, 30 Guilford Street, London WC1N 1EH
- Dr D P M Symmons, ARC Epidemiology Research Unit, Stopford Building, University of Manchester, Oxford Road, Manchester
- Dr C M Taylor, Birmingham Children's Hospital NHS Trust, Laboratory of Enteric Pathogens, Ladywood Middleway, Birmingham B16 8ET
- Dr J Tripp, Dept of Child Health, Postgraduate Medical School, Royal Devon & Exeter Hospital, Barrack Road, Exeter EX2 5DW
- Ms P Tooke, Department of Paediatric Epidemiology and Biostatistics, Institute of Child Health, 30 Guilford Street, London WC1N 1EH
- Dr P Verloove-Vanhorick, TNO Prevention and Health, P O Box 2215, 2301 CE Leiden, Netherlands
- Dr C Verity, Child Development Centre, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ
- Dr R Von Kries, Institute für Sozial Paediatric und Jugendmedizin der Ludwig-Maximilians Universität München, Germany
- Ms E Wadsworth, Institute of Child Health, Royal Hospital for Sick Children, St Michael's Hill, Bristol BS2 8BJ
- Dr R Will, The National Creutzfeldt-Jakob Disease Surveillance Unit, Western General Hospital, Edinburgh
- UK Haemophilia Centre, Churchill Hospital, Headington, Oxford OX3 7LJ
- Dr J Wynne, Belmont House, Clarendon Wing, Leeds General Infirmary, 3-5 Belmont Grove, Leeds, West Yorkshire LS2 9NS
- Dr H P Zimmerman, Swiss Paediatric Surveillance Unit, Federal Office of Public Health, Division for Epidemiology and Infectious Disease, CH-3003 Bern, Switzerland