British Paediatric Surveillance Unit

11th Annual Report

A unit within the Research Division of the

Royal College of Paediatrics and Child Health

1996-1997

The British Paediatric Surveillance Unit always welcomes invitations to give talks describing the work of the Unit and makes every effort to respond to these positively.
Enquiries should be directed to the British Paediatric Surveillance Unit office.

The Unit positively encourages recipients to copy and circulate this report to colleagues, junior staff and medical students.
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ISBN 1 900954 14 1

Published September 1997 by the:
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British Paediatric Surveillance Unit - 11th Annual Report, 1996-97
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Acknowledgements

The British Paediatric Surveillance Unit (BPSU) wish to thank Children Nationwide Medical Research Fund for its generous core financial support, which ended in 1996. Without such support over the past nine years the Unit could not have developed as successfully as it has. Thanks should also go to the anonymous trust that has granted core support for the next two years, and to Allen & Hanburys for supplying protocol booklets.

In 1996, the BPSU held its second scientific meeting. We extend our thanks to Pasteur Merieux MSD and Serono for their support.

We particularly thank members of the Royal College of Paediatrics and Child Health, the Faculty of Paediatrics of the Royal College of Ireland, and the many other clinicians who have contributed reports and data to the BPSU, and through it to the researchers who use the Unit. Without these contributions the BPSU would not be the world leader that it is.

British Paediatric Surveillance Unit Executive Committee
September 1997

Foreword

Back to the future

Last year we looked back and celebrated ten years of Surveillance Unit activity. This year the Unit is looking forwards and planning its activities as part of our new Royal College of Paediatrics and Child Health. However one important decision made this year has reminded us of the past. It was decided that our name should revert from 'The British Paediatric Association Surveillance Unit' (BPASU) to the original 'British Paediatric Surveillance Unit' (BPSU). The return to the original name has emphasised the continuity of the work of the Unit and its pioneering role in paediatric surveillance. A few years ago the name was changed to BPASU in order to recognise the central importance of paediatricians in maintaining the viability of this important project. This situation has not changed. To quote last year's report, **paediatricians *are* the Surveillance Unit.** The amazingly good response rate to the monthly orange card continues to emphasise that paediatricians value and support the work of their Unit.

The BPSU is looking forward to continuing its development within the Research Division of the new College and to strengthening links with other key participants. It has received tremendous help and support from the Communicable Disease Surveillance Centre and the rest of the Public Health Laboratory Service, the University of London's Institute of Child Health (ICH), the Royal College of Physicians (Ireland) and the Scottish Centre for Infection and Environmental Health. The two Medical Advisers, Margaret Guy and Angus Nicoll, provide essential support. Their sessions are funded by their employers - the Brent and Harrow Health Authority and the Public Health Laboratory Service. The breadth of support for the Unit has been essential for its development and will continue to be fundamentally important in the future.

The BPSU has provided a model for other surveillance units in the British Isles and elsewhere. The British Neurological Surveillance Unit is now well established and so is the British Ophthalmological Surveillance Unit. The adult gastroenterologists are planning a surveillance system. This provides the opportunity for fruitful collaboration. We have maintained close contact with paediatric surveillance units abroad. Angus Nicoll, the BPSU Medical Adviser, has been to Ottawa as special advisor to the Canadian Paediatric Surveillance Programme. A representative from the Australian Paediatric Surveillance Unit (APSU) visited last year. The findings of the APSU study of childhood dementia were most helpful when the BPSU Executive Committee was evaluating the proposal for the British study of PIND (progressive intellectual and neurological deterioration).

The BPSU has been looking towards Europe. Richard Lynn, the BPSU Scientific Coordinator, submitted a Biomed application for European Committee funds: unfortunately this was unsuccessful, despite the fact that it obtained good scores from the referees. Last year Richard Lynn and Angus Nicoll attended the Elsinor meeting of the European Society for Paediatric Infectious Disease. The plan is to continue to seek funds for developments in Europe and to maintain other academic and international contacts, possibly by fostering an 'International Association of Paediatric Surveillance Units'. This would aim to share information between paediatric surveillance units and consider the organisation of joint projects giving added value to the work that is taking place within countries.

These international plans are exciting, but it remains a priority to facilitate relatively small but important studies from individual paediatricians. The message is: do not be put off just because you do not hold a large grant. Please approach the Scientific Coordinator, or another member of the BPSU Executive Committee if you have an idea for a project and we will try and take it forward. Unfortuntately, it is relatively difficult to obtain grant money for the central organisation and running of the unit. For most of its time, the BPSU has been financially supported by Children Nationwide Medical Research Fund. This support continued for nine years and the Unit is particularly grateful to Sir Eric Stroud, who played an important part in this. Unfortunately that funding has now ceased. Partly for that reason it has been necessary to increase the fees for researchers. However, together with John Osborne, the College Honorary Treasurer, we are endeavouring to obtain core funding for the Unit. The aim is to facilitate good research projects even if local researchers have difficulties in obtaining funds.

This annual report shows that studies of considerable public health importance have been undertaken by the Unit in the last year. It is one of the aims of the Unit to raise the awareness of epidemiological and public health issues. It is important to disseminate knowledge to those working for the maintenance of child health. The Unit's second scientific meeting was therefore organised at the Royal College of Physicians last December. The day was stimulating and enjoyable. Our plan is to repeat such meetings when we can, possibly in another centre outside London. Meanwhile we would like to involve junior staff in order to give them experience of epidemiology and research. The Research Division and the BPSU have therefore maintained a presence at the annual meeting in April and have organised research workshops during that time.

This is one way in which the Surveillance Unit works within the Research Division, supporting the broader activities of the College.

In conclusion, I would like to look back and give some well-deserved thanks. Many thanks to Dr Una MacFadyen for the work that she did whilst she was a member of the Surveillance Unit Executive Committee. Indeed all the committee members are to be congratulated for their continued support - the Executive Committee meets every month and generates a lot of work. Professor Sir Roy Meadow deserves our thanks and congratulations for steering the Surveillance Unit through the transition from BPA to Royal College. As Professor Baum takes over as our President, we look back with thanks for all the effort that he has put into the Unit over the years. We can now look forward to his continuing support for the activities of the Surveillance Unit within the College. We hope that with the support of all College members we will be able to build on the considerable achievements of the Surveillance Unit since it was first set up as the BPSU.

Dr Christopher Verity,
Chairman, BPSU Executive Committee

1 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, observers from the Department of Health and the Office for National Statistics also attend 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 1996. Reference is also made to studies and activities which have commenced in 1997.

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.

2 How the surveillance system works

The surveillance scheme involves the active reporting by paediatricians of children affected by any of the conditions currently included in the reporting scheme. To be eligible for inclusion in the scheme, the condition under study must be sufficiently rare to require the ascertainment of cases at a national level.

Any researcher may apply to use the BPSU to identify cases of a particular condition. However, before a condition can be included in the scheme, the study must be approved by the BPSU's Executive Committee. The number of conditions under surveillance at any one time is usually limited and priority is given to the study of conditions of particular public health importance.

Selection of studies for inclusion in the scheme

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 paediatric department.

The number of conditions under surveillance is usually limited to 12 and there is keen competition for places on the BPSU card. Occasionally, the capacity of the reporting card has been increased to accommodate 14 rather than 12 conditions. The Unit receives an average of 30 general enquiries about potential studies each year; only a minority of which are eventually incorporated into the reporting card. About 25 studies are currently in various stages of development.

The BPSU has recently adopted a procedure to process applications with minimal delay. The Executive Committee meets monthly or six weekly to achieve this and the Scientific Coordinator, the Medical Advisers and individual committee members work in between meetings to assist applicants. The Unit sees itself as having a particular responsibility to assist paediatricians in producing good, high quality and practical studies. The procedure consists of two phases: in Phase One, a short study protocol is submitted, covering no more than two sides of A4 paper. This should include the background to the proposed study, a case definition, 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.

For a number of reasons many studies are found to be unsuitable at the Phase One stage. The condition may be too common and therefore 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 are obtainable more easily elsewhere. If a study is not accepted, the Executive Committee always tries to advise the applicant on alternative means of undertaking the work. In addition some studies present insuperable practical difficulties. Once the Executive 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. The applicant presents the details to the Executive Committee which comprises consultant paediatricians (general and specialist), epidemiologists and specialists in public health. Factors which increase the likelihood of a study being accepted are listed in the box.

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 if appropriate.

If necessary the BPSU will help potential investigators, especially those with less experience in research methods, to develop potentially valuable studies.

The reporting system

Participants in the reporting system include consultant paediatricians who are either members of the Royal College of Paediatrics and Child Health 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 other specialists. 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. This has improved the level of ascertainment of cases of biliary atresia and haemophagocytic lymphohistiocytosis and continues to do so for HIV/AIDS and congenital rubella.

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 preceding calendar month. Scottish paediatricians return their completed cards via the Scottish Centre for Infection and Environmental Health. Respondents are asked to keep a tear off section of the card in order to hold the disease name and which, as a reminder, is completed with patient and disorder details.

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 three 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. Table 2 (page 12) shows the number of cases reported to the BPSU from its inception until the end of 1996 for all the conditions under surveillance during 1996. 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 July 1997, only 115 (6%) of the 2569 cases reported up to the end of 1996 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 3 (page 12) summarises the outcome of the follow up of all cases reported to the BPSU by the end of 1996 and provides evidence for the high level of accuracy of reporting by participating clinicians. By the end of July 1997, only 535 (21%) of the 2569 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 July 1997).

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. 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.

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 on cases reported to the Unit. The first complimentary data source to be used was laboratory reports of infectious disease to the PHLS. 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's 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.

In an analysis of those BPSU studies that included multiple sources, the BPSU proportion of sole ascertainment ranged from 20% for the MMR-Meningitis survey in 1991 to an on-going 95% for HIV/AIDS, with an average of 75-80%. It could be argued that where BPSU ascertainment is so low, actual involvement by the Unit is not necessary. Particularly, this depends on whether a study's objectives require complete ascertainment of all cases or whether they can be met by a sample of cases. Though it can also be argued that the awareness of the BPSU card promotes reporting through other systems, this was the case for SSPE, and the reason for placing SSPE back on the card in late 1995. Even where the BPSU provides only a low proportion of new cases the dual reporting of cases often highlights errors in data or initially reported cases. However, dual reporting can bring its own problems, cases may not always be easily linked and reporters rightly become irritated if they are asked to give details on a case more than once.

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 overhead costs of coordinating the study. In 1996 the minimum sum was £185 a month which met 40% of the Unit's total running costs. This figure has been revised from September 1997 to £210 a month. This will be the first increase in over two years and will re-coup about 50% of the Unit's running costs. Applicants will also be encouraged to include the full running costs of the BPSU as part of their study in any research grants to outside bodies, eg. Medical Research Council or Department of Health.

The remainder of the Unit's costs in 1996 were met through an anonymous donor and Children Nationwide Medical Research Fund. 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.

The second BPSU scientific meeting, held in December 1996, was supported by Pasteur Merieux MSD and Serono.

Funding to the European Commission through the Biomed programme for a concerted action into rare disease, enabling better communication between the existing European surveillance units was sought. Unfortunately, this was turned down and alternate sources of funding will be needed if this activity is to be extended.

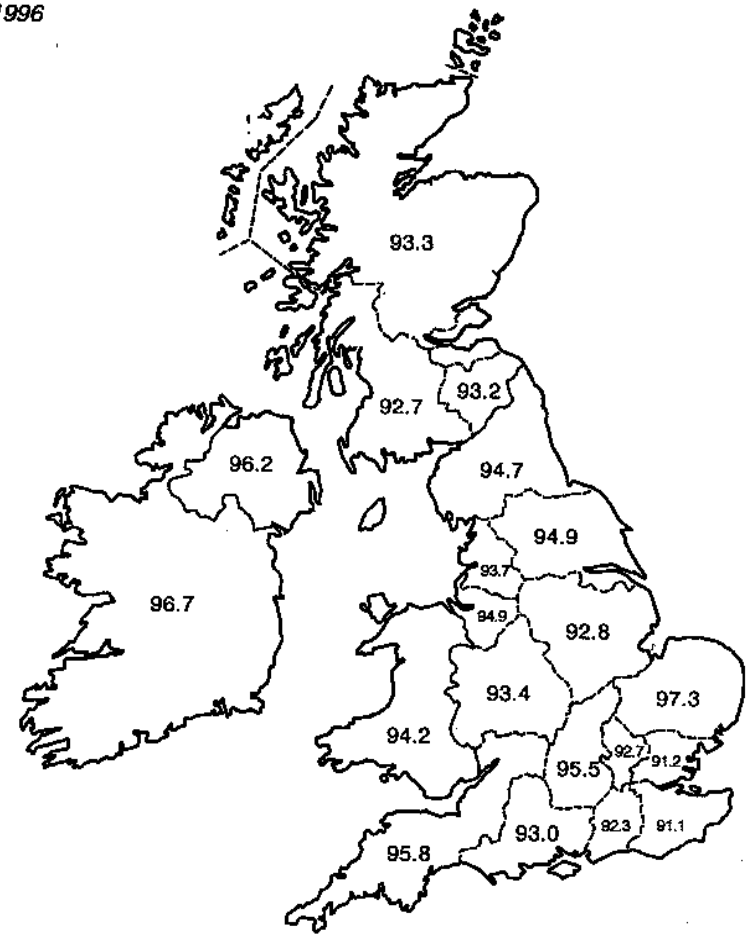
3 Surveillance activities in 1996

Though 1996 only saw one new study commence (neonatal meningitis) it was still a busy year for the Unit. Fifteen study applications were received 12 of which are actively being considered with a further 15 studies in various stages of development. The results of the increase in applications is seen in the number of studies which have commenced in 1997, three to date and several provisionally approved. By the end of 1996, 32 studies had been completed since the BPSU began in June 1986 - those completed prior to 1996 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 1996 relating to these studies and the Unit's work, totalled 20, including presentations at the European Society for Paediatric Infection and Disease; these are listed in Appendices B and C. Finally, in December the BPSU held its second scientific meeting, *Paediatric Surveillance in Practice*, this was a great success, being attended by over 100 clinicians, a full report of which is given in Chapter 9.

Participation in the scheme during 1996

The BPSU ascertains the names of new consultants through the RCPCH membership office, BMJ adverts or through personal communication. Clinicians no longer actively seeing patients are removed from the mailing list. The number of consultant paediatricians participating in the BPSU rose from 1445 to 1596 by December 1996, an increase of over 10% on the year. The increase is also partially due to the identification of consultants through the RCPCH 1995/96 manpower census. By validating against the BPSU mailing list a further 60 consultants, previously missed, were added, the majority of whom worked in the community or were senior lecturers (honorary consultants) seeing patients. This suggests that the sources used by the Unit had underascertained by approximately 5%, though this is less than the 7-8% suggested by a recent independent report, which used the 1993 manpower census as its source of

Figure 1 *Average orange card return rate (%) by area, 1996*



Overall average orange card return rate = 94.0%

validation (see Appendix C). In some cases paediatricians are excluded as they do not undertake clinical work, or else colleagues report on their behalf. It is hoped that with the RCPCH taking over the administration of consultant appointments, underascertainment will be kept to a minimum. The BPSU mailing list also includes selected groups of consultants other than paediatricians i.e., pathologists, cardiologists, and clinical geneticists.

Compliance rates for returning the orange cards remains high, - the overall response rate for 1996, calculated as a proportion of orange cards returned, was 94.0%, similar but slightly down on 1995. This may have been due to several localised postal disputes throughout the year. Monthly response rates ranged from 90% in July 1996 to 95.4% in April 1996, with a median of 93.8%. Of those responders not returning cards less than 1% are persistant.

As in previous years, reporting rates varied considerably across the country, as is shown in Figure 1. Yet again, East Anglian paediatricians achieved the highest response rate - 97.3%. Compliance was lowest in South East Thames at 91.1%.

Conditions included in the scheme during 1996

During 1996, twelve conditions were the subject of surveillance. Four studies were completed and one study commenced. The studies are listed in Table 1. The main findings of the 1996 and 1997 studies, which are described in full in Chapter 5/6, are summarised on page 10. The study on adverse neonatal outcomes of delivery or labour in water, completed in early 1996, is described in the 10th Annual Report.

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. Figure 2 demonstrates that 75% of participants reported no cases in 1996, 24.3% reported between one and four cases and only 0.7% reported more than five cases. The orange card currently carries a significant number of disorders affecting neonates thus currently neonatologists are proportionally having to report more cases; their continued support is most appreciated.

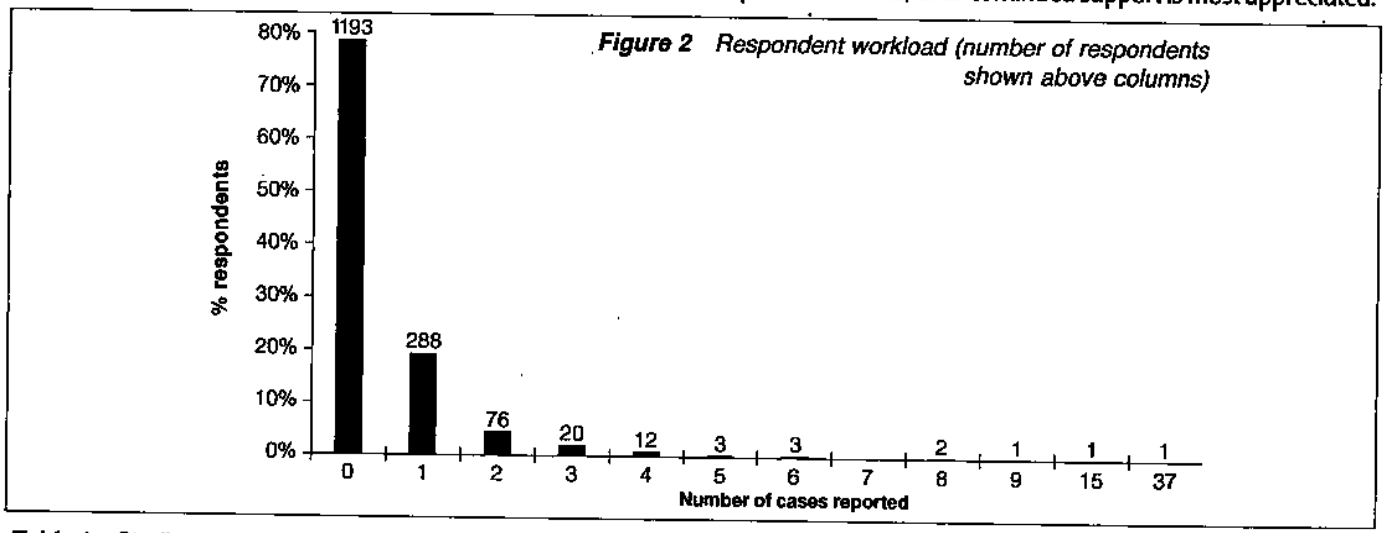


Figure 2 *Respondent workload (number of respondents shown above columns)*

Table 1 *Studies underway in 1996*

Page	Study	Principal researchers	Research institutions
13	Cerebral oedema following DKA*	J Edge, D Dunger	John Radcliffe Hospital
14	Congenital cataract	J Rahi	Great Ormond Street/ICH (London)
15	Congenital rubella*	P Tookey, C Peckham	ICH (London)
16	Congenital syphilis	A Nicoll, T Lissauer	PHLS, St Mary's Hospital (London)
17	HIV/AIDS infection in childhood*	P Tookey, A Nicoll, D Goldberg	ICH (London), PHLS, SCIEH
19	*Haemophilus influenzae* infection*	P Heath, M Slack, R Moxon, N Begg	PHLS, National Haemophilus, Ref. Lab. Oxford
20	Medium chain acyl-CoA dehydrogenase	R Pollitt, J Leonard	Sheffield Children's Hospital
21	Neonatal meningitis*	S Halket, D Holt	Queen Charlotte's & Chelsea Hospital
22	Pyridoxine dependency	P Baxter	Sheffield Children's Hospital
24	Reye's syndrome*	S Hall, R Lynn	Sheffield Children's Hospital/BPSU
26	Subacute sclerosing panencephalitis*	E Miller, N Begg	PHLS

* Studies still in progress to September 1997.

4 Main findings of studies undertaken in 1996

Ongoing studies

Cerebral oedema & death following diabetic ketoacidosis
(page 13)
Cerebral oedema is the most serious complication of diabetes in children. Often it results in death or handicap. The aetiology of the condition and its optimal management are unclear and are the main objectives for this study which has only been underway since late 1995. To date complete reports of cerebral oedema have been confirmed for 16 cases, three of which resulted in death.

Congenital cataract
(page 14)
Congenital cataract can cover a range of visual impairments from mild handicap to blindness. Gathering epidemiological, referral and clinical data on cases occuring in the UK is the subject of this study and is essential for making recommendations for early detection and management of this rare condition. Like many of the BPSU studies additional sources apart from paediatricians were used. Two hundred and eleven cases were reported in just over a year, 152 from paediatricians. In the other cases the first presentation was to an ophthalmologist. Patterns of referral and underlying aetiology (where known) are now being analysed.

Congenital rubella
(page 15)
The incidence of congenital rubella has been low in recent years. However there have already been nine reports of children born affected with congenital rubella syndrome in 1996, the highest total since 1990. Foreign born mothers who have missed out on routine rubella immunisation are a less important feature than in previous reports, and seven of the cases are severely affected infants of British born mothers. This has been attributed to recent outbreaks of rubella in young adults in the UK, especially males, too old to have been protected by routine immunisation with the combined measles mumps rubella (MMR) vaccine which began for both sexes in 1988 or the measles rubella (MR) campaign of 1994. Numbers of 1996 born cases are almost certain to increase as less obviously affected children, for example those with isolated deafness, come to light.

Congenital syphilis
(page 16)
Sixteen confirmed reports of congenital syphilis in children have been received through the BPSU system over three years. Most of these were detected through maternal antenatal screening and the children will probably not be affected as the infection was treated. The reasons for the low numbers of cases are now under investigation looking at the levels of syphilis among pregnant women and a policy analysis on antenatal screening in pregnancy is in preparation.

HIV/AIDS infection in children
(page 17)
Continuing surveillance for HIV and AIDS in children demonstrates that the group of children infected with HIV in the 1980s through contaminated blood products have now either moved into adulthood or have died. Transmission of HIV through blood products all but ceased some years back in the UK and now almost all children with this lethal condition are being infected through mother to child (vertical) transmission of the virus. Interventions that substantially reduce the risk of vertical transmission have been available for some time. These are all reliant on maternal HIV infection being diagnosed well before birth and unfortunately surveillance data suggest that in England over 80% of these infections remain undiagnosed by the time of birth. The situation is worst in London where it is estimated that over twenty children could be saved from HIV infection annually if current policies to offer HIV testing to all pregnant women in London were implemented.

Invasive *Haemophilus influenzae* infection
(page 19)
Surveillance for invasive *Haemophilus influenzae* has been underway since 1992 when vaccination against *Haemophilus influenzae* type b (Hib) was introduced in the UK. Initially looking for cases of apparent vaccine failures surveillance extended to all cases of invasive *Haemophilus influenzae* disease in children. From these data vaccine efficacy has been estimated at 99.2% for children aged 5 to 11 months declining only marginally to 97% in those aged 3 years. Among children showing true vaccine failure a significant number were found to have underlying abnormalities such as an immunoglobulin deficiency. Surveillance therefore continues to demonstrate satisfactory high levels of protection from Hib vaccination in older children despite the lack of a booster vaccine dose which is given in other countries. It is also concluded that children who have suffered invasive Hib disease despite vaccination deserve further investigation.

Medium chain acyl-CoA dehydrogenase deficiency (MCAD)
(page 20)
MCAD is an inborn metabolic disorder with a variable presentation which can include profound hypoglycaemia, 'sudden infant death syndrome (SIDS)' and 'Reye' syndrome. Over two years 49 new cases were reported with ages of diagnosis that ranged from 2 days to 12 years. In nearly a third of these cases there was a family history and some asymptomatic cases were diagnosed because of a symptomatic case in a relative. These results are being incorporated into a Health Technology Assessment for routine neonatal screening.

Neonatal meningitis
(page 21)
Neonatal meningitis is one of the most important infections of young babies, often resulting in death or handicap. This study is repeating elements of a study of meningitis in children undertaken a decade ago, looking at any change in the pattern of infection, the causative organisms and treatment. In under a year of reporting 211 reports of neonatal meningitis have been received, though data has only been received on a minority of these cases. Of the cases where data were available bacteria were isolated in 41 cases, 21 of which featured Group B haemolytic streptococci.

Pyridoxine dependency
(page 22)
Pyridoxine dependency is a rare inherited cause of seizures starting in early childhood. In the first year of surveillance eighteen cases of pyridoxine deficiency have been received, four of which have been proved to be definitive, as shown by formal trials of withdrawal of therapy. There has been a predominance of cases among younger children which may represent increasing awareness of this condition among paediatricians perhaps because of instituting surveillance.

Reye's syndrome
(pages 24)
In the year to July 1996, eighteen case reports of Reye's syndrome (RS) were received, all but one through the BPSU. Follow ups have been received on all but one. Fifteen reports had clinical and pathological features compatable with RS. One case was due to an underlying metabolic disorder. Numbers of Reye's cases have fallen substantially since surveillance for this condition started in 1981, seemingly in association with the cessation of the use of aspirin among children (under age 12 years) in 1986. However, the numbers (4) and proportion (30% of those with information on pre-admission medication) of cases reporting pre-admission aspirin exposure in 1995/96 were the highest since 1986/87. There were also seven deaths in 1995/96, the highest number since 1989/90.

Subacute sclerosing panencephalitis (SSPE)
(page 26)
SSPE is a consequence of earlier infection with wild measles virus. Cases can occur many years after the initial infection and therefore reflect historical incidence of measles. Forty two cases of SSPE have been ascertained since 1989. Ten of the cases were of Asian ethnic group and six were first generation immigrants from countries where measles infection is endemic and probably represent the result of infections acquired abroad. Over the long term numbers of cases of SSPE have declined substantially as the incidence of measles in the UK has declined. In the period 1993-6 the average number of reports of cases was three. This compares with an annual number of cases of between 15 and 20 in the 1970s.

New studies commenced in 1997

Haemolytic uraemic syndrome - HUS
(page 29)
In the UK the main cause of HUS is infection with *E.Coli 0157*. HUS was previously on the BPSU card in 1986-9. It was placed back on the card in response to the public health emergency surrounding *E.Coli 0157* in 1996/7 and in anticipation of the Pennington Report on the outbreak of infection in adults in Lanark, Scotland in 1996.

Hepatitis C infection
(page 30)
Hepatitis C infection was placed on the BPSU card as part of a programme of studies of hepatitis C in the UK sponsored by the Department of Health. Eventually the study will describe the natural history of hepatitis C infection in children which at the moment is essentially unknown.

Progressive intellectual and neurological degeneration (PIND)
(page 31)
There are a diverse group of conditions that cause children to suffer from progressive intellectual deterioration. This will be the first study of the epidemiology of children with this presentation in the UK. Paediatricians are being asked to report children both where a diagnosis has been made (for example Rett syndrome, one of the commoner causes of PIND) and where no diagnosis has been made. A major rationale of this study is that if new variant CJD is appearing in children it will do so in children with PIND. This work was initiated with Department of Health sponsorship in response to the public health emergency over CJD in 1996/7.

Table 2 *Cases reported from June 1986 - December 1996 of conditions under surveillance during 1996 (cases confirmed by July 1997 shown in brackets)*

Condition under surveillance	Date when reporting began	Reports (confirmed cases) June 1986 to Dec 1989	Jan 1990 to Dec 1992	Jan 1993 to Dec 1995	1996
HIV/AIDS	June 1986	137 (90)	495 (386)	359 (214)	160 (93)
Reye's syndrome	June 1986	149 (76)	71 (31)	57 (18)	13 (8)
SSPE	June 1986	84 (50)	55 (29)	28 (14)	6 (2)
Congenital rubella	Jan 1991	– –	43 (27)	29 (12)	23 (12)
Hi infection	Sept 1992	– –	25 (20)	146 (106)	72 (48)
Congenital syphilis	July 1993	– –	– –	18 (14)	4 (4)
MCAD	March 1994	– –	– –	93 (51)	8 (4)
Pyridoxine dependency	Sept 1995	– –	– –	15 (9)	26 (8)
Congenital cataract	Sept 1995	– –	– –	77 (47)	175 (115)
DKA	Oct 1995	– –	– –	24 (4)	24 (9)
Neonatal meningitis	July 1996	– –	– –	– –	153 (94)
Total		**370 (216)**	**689 (493)**	**846 (489)**	**664 (397)**

Tables exclude previously completed studies (see page 42).

AIDS/HIV Acquired immune deficiency syndrome/human immunodeficiency virus (AIDS/HIV): 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 *Haemophilus influenzae* infection, pre Oct 1995 **Hib vaccine failures only.**

MCAD Medium chain acyl-CoA dehydrogenase.

DKA Cerebral oedema following diabetic ketoacidosis.

Table 3 *Outcome of follow up of the cases reported up to December 1996 of conditions under surveillance during 1996*

Condition under surveillance	Valid reports (%)	Invalid reports: Duplicates	Errors	(Total %)	Not yet known (%)	Total reports
HIV and AIDS	783 (68)	147	193	(30)	28 (3)	1151
Reye's syndrome	133 (46)	41	106	(51)	10 (4)	290
SSPE	95 (53)	27	30	(30)	21 (17)	173
Congenital rubella	51 (54)	17	23	(41)	4 (5)	95
Hi Infection*	174 (72)	13	53	(27)	3 (1)	243
Congenital syphilis	18 (82)	0	3	(14)	1 (5)	22
MCAD	54 (53)	21	26	(47)	0 (0)	101
Pyridoxine dependency	17 (41)	4	14	(44)	6 (15)	41
Congenital cataract	162 (63)	33	45	(31)	12 (6)	252
DKA	13 (33)	11	23	(56)	1 (10)	48
Neonatal meningitis	94 (56)	11	19	(18)	29 (26)	153
All	**1594 (61)**	**325**	**535**	**(33)**	**115 (6)**	**2569**

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

5 Surveillance studies undertaken in 1996

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 per 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. Furthermore, the aetiology is not understood and even with optimum management by current standards, cases still occur.

Retrospective studies suggest that cerebral oedema is more common in newly diagnosed diabetes, especially in children under 5 years of age. Possible contributory factors may be severity of DKA, the rate and/or quantity of intravenous fluid administration, a fall in plasma sodium concentration and hypoxia from 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.

The BPSU is comparing the clinical course of cases of cerebral oedema with controls with DKA but without cerebral oedema, ascertained by a separate reporting mechanism. This is the first large prospective case-control study of this condition.

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 - November 1998.

Analysis

From October 1995 until February 1997, 54 returns were made to the BPSU. Questionnaires have been returned on all but three. Six reported retrospective cases, occurring before October 1995, ten were reporting errors or non-cases and ten were duplicate reports. Of the remainder, two were deaths during ketoacidosis which were not due to cerebral oedema. There have been 16 definite cases of cerebral oedema (three of which resulted in death). In addition, there have been ten cases of unexplained deterioration of conscious level but without definite signs of raised intracranial pressure. The investigators intend to continue collecting cases until November 1998.

In order to obtain controls for the case-control study, we are also receiving monthly notifications of all cases of DKA admitted in England, Scotland and Wales, from 250 paediatricians around the country. So far, over 1800 cases of DKA have been notified. From these we shall be able to choose matched controls for the cases of cerebral oedema. If there are any paediatricians who look after children with diabetes and have not been contacted, the investigators would be very grateful if they could be contacted.

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.

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Congenital cataract

Background

Despite considerable recent progress in the surgical and optical management of congenital and infantile cataract, a significant proportion of treated children continue to be registered blind (up to 30% in the United States of America). Congenital and infantile cataract can also cause mild or moderate visual impairment which may go unrecognised, particularly if it is unilateral. In children with multiple disabilities, it may be the most readily treatable eye disorder and the improved vision that results from treatment may contribute to the child's overall development.

Early detection and treatment of congenital and infantile cataract is probably the most important of a number of factors relevant to good visual outcome. In humans the 'critical period' during which interventions to prevent the development of irreversible amblyopia are likely to be most successful is from birth to 10 weeks of age. The best reported visual outcomes are in children who undergo surgery early within this period. Early surgical intervention requires detection and ophthalmic referral in the neonatal period. Children not identified by specific neonatal examination will present at different ages and to various health professionals, depending on the severity of visual loss and the presence or absence of other ocular or systemic disorders. The current patterns of presentation and detection in the United Kingdom, including the age at presentation, to whom the child first presented, and the reason for first presentation are unknown.

Epidemiological data on congenital and infantile cataract are important to the development of effective recommendations about its early detection and ophthalmic management. The main sources of data on congenital and infantile cataract in the United Kingdom are registers of partial sight and blindness, surveys of children attending schools for the blind and clinical case series. All these sources are limited in terms of completeness, potential bias or detail and most studies based on them have been retrospective. Hospital data suggest ophthalmologists in the United Kingdom see about 150 new cases each year but the birth prevalence is unknown.

Numerous causes of congenital and infantile cataract have been reported but it is not known if the underlying cause is associated with the patterns of detection or of ophthalmic referral. Surgical and optical treatment techniques for congenital and infantile cataract have advanced in recent years but there are no uniform treatment policies for either unilateral or bilateral cases. Different centres have reported the results of their management regimens. Many reports involve small numbers of patients and provide limited data.

Research questions

1. To estimate the birth prevalence of congenital and infantile cataract in the British Isles.
2. To determine the national and regional patterns of presentation and ophthalmic referral.
3. To assess aetiology in incident cases and to determine the proportion attributable to preventable causes.
4. To determine the factors associated with good visual outcome.

Case definition

Any child under 16 years of age who has suspected or confirmed cataract(s), which may be unilateral or bilateral and of any severity. This includes any child who has been treated for cataract(s) in the past four weeks.

Study duration

The study began in October 1995 and ended in October 1996.

Current Status

The 13 month case ascertainment period for the study ended in September 1996. Case validation is complete and preliminary analyses are being undertaken.

Case reporting through the BPSU

A total of 248 reports were received from paediatricians through the BPSU. Of these, 37 were duplicate reports.

The nature of the 211 reports which remain after exclusion of duplicates is shown in Table 4.

In 5% (7) of the 152 cases reported by paediatricians, the BPSU was the sole source of reporting with all other cases being reported by ophthalmologists and in some cases, through another additional source. In 18% (27) of the cases, the child first presented to an ophthalmologist outside the study case ascertainment period and these cases will be excluded from the estimate of incidence. These cases will be included, as appropriate, in the cohort of cases in whom outcomes of treatment will be assessed.

The study has used multiple independent sources of case reporting which will allow capture-recapture techniques to be used to estimate the degree of underascertainment.

Planned analysis

A unique and nationally representative cohort of cases has been created and detailed analyses of the patterns of presentation/detection and pattern of underlying or associated causes of cataract are being undertaken. These will be reported to paediatricians in due course. The detailed analysis of information on presentation to and detection of children with cataract by health professionals may be of particular interest.

Table 4 Congenital Cataract Study

Total Reports	Case	Error		Unable to trace	
(excludes duplicates)		No cataract	Did not meet case definition	No reply from paediatrician	Paediatrician unable to trace case
211	152 (72%)	14 (7%)	24 (11%)	15 (7%)	6 (3%)

Preliminary analysis suggests that the incidence of congenital/infantile cataract is higher than previous estimates based on routinely collected data.

Acknowledgements

The investigators thank all reporting paediatricians for their interest in the study and for providing information on their patients. They are grateful to the Executive Committee of the BPSU for the opportunity to carry out the study. Finally they acknowledge the generous support of the Medical Research Council (UK), Children Nationwide Medical Research Fund and the British Council for the Prevention of Blindness.

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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 has been included in the BPSU reporting scheme since 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, 96 reports have been made through the BPSU. Thirteen of these reports were from Eire or Northern Ireland, and included four children with confirmed congenital rubella (one born in 1989 and three in 1996), seven duplicate or error reports and two children who had been previously reported via another source; reports from Ireland are followed up but not included in the NCRSP registry figures. Of the 83 reports from England, Scotland and Wales, 41 are confirmed, previously unreported cases of congenital rubella, one is a possible case which cannot be confirmed because laboratory information is lacking, and seven have already been reported via another source (audiologists, virologists and CDSC). The remaining 34 reports were duplicates (17), reporting errors (16) and one where further information could not be obtained.

Altogether 869 children with confirmed congenital rubella are registered with the NCRSP. Seventy six per cent of those born since the beginning of 1990 (32 out of 42 cases, see Table 5) were first reported through the BPSU.

The incidence of congenital rubella is now very low: most infected infants are born to women born abroad who came to the UK as susceptible adults, or who arrive in the UK having acquired rubella in early pregnancy abroad (imported cases, seven recorded since 1990). However for 1996, following a number of outbreaks of rubella infection mainly in young males, nine confirmed cases have already been reported, including seven severely affected infants born to British-born women. All these infants were born to women whose infection occurred in the first few weeks of pregnancy; they are therefore likely to represent only a proportion of infected infants. Infants whose mothers acquired rubella at a slightly later stage of pregnancy are likely to have single defects, particularly hearing loss, which may not yet have become apparent.

It is essential that case ascertainment is as complete as possible. Paediatricians and other reporters are asked to notify to the BPSU all children suspected of having congenital rubella, whether or not they have the associated typical defects. The investigators continue to be grateful for the cooperation and efforts of reporters.

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Table 5 *Confirmed congenital rubella births reported to the NCRSP 1971-1996**

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*	*0*	*9*
Total	**47**	**822**	**869**

* The data for recent years are provisional
** Includes one set of twins

Congenital Syphilis

Background

The BPSU survey of congenital syphilis began in July 1993. Its aim has been to undertake surveillance for congenital syphilis in the United Kingdom and the Republic of Ireland. Previously, the only surveillance of congenital syphilis was through the genitourinary medicine (GUM) clinics, and it was unclear whether all affected children might be attending such facilities.

The importance to public health of this survey has increased since it began, as suggestions have been made that antenatal serological screening for syphilis should cease[1]. It is thought that all women who receive antenatal care in the United Kingdom are screened for evidence of syphilis and other treponemal infections, such as yaws and pinta, which are serologically indistinguishable. Although national data suggest that infectious syphilis in women is uncommon in the United Kingdom, it still occurs. Totals of new cases in women between the ages of 15 and 59 attending GUM clinics in England during 1993, 1994 and 1995 were 108, 110 and 96 respectively. Moreover, the current levels of infection may not remain low indefinitely. In the United States, a substantial epidemic of adult syphilis and failure to provide universal antenatal care (including serologic screening) has resulted in a substantial epidemic of congenital syphilis. This has abated but more recently, there is now a massive resurgence of adult syphilis in the former USSR and adjoining parts of Eastern Europe and cases from this origin are now beginning to be detected in the UK[2].

Objective

To determine the minimum incidence of congenital syphilis in children, detect possible maternal and other risk factors, and look for trends while the study continues.

Case definition

A confirmed case is an infant, stillbirth, or child under 16, in whom direct evidence of *Treponema pallidum* is found.

A **presumptive case is either** an infant, stillbirth, or child under 16, whose mother had untreated or inadequately treated syphilis at the time of delivery **or** an infant, stillbirth, or child under 16, with a reactive specific treponemal test (TPHA or FTA-Abs **not** just VDRL or RPR) and evidence of infection.

A **possible case** is an infant, stillbirth, or child under 16, treated for syphilis, who does not fill confirmed or presumptive criteria.

Duration

The study commenced in July 1993 and ended in July 1996.

Results

Preliminary analysis indicates that between July 1993 and July 1996, twenty-five reports were made - six in 1993, three in 1994, seven in 1995 and, nine in 1996. Six reports were not confirmed as cases when further information became available. Of the nineteen confirmed cases, ten were "presumptive" and nine "possible". All except one came to medical attention via

maternal screening. The exception was a black-Caribbean child born in November 1995 (presumptive case) who came to medical attention because of hepatosplenomegaly. The mother was then found to be seropositive. In addition one stillbirth attributed to syphilis was reported by laboratory surveillance.

The low numbers may be explained in five ways: There may be few paediatric cases to diagnose and report, (either because there are no cases of infectious syphilis among pregnant women or because antenatal screening and treatment of mothers is effective in preventing vertical transmission), there may be a failure to make the paediatric diagnosis (especially in "possible" cases without symptoms), diagnosed cases may not be reported, and diagnosed cases may not be seen paediatricians (it is known that some are referred to specialists in genitourinary medicine with their mothers).

The research team is completing investigations of the low numbers coming through the BPSU scheme through collaboration with the British Cooperative Clinical Group (BCCG), a group of GUM physicians in the UK, with which an equivalent survey was completed in early 1997. This is analogous to the BPSU scheme, but was looking for cases of treponemal infection (including syphilis) requiring treatment, in pregnant women. These data provide a minimum estimate of how many infections are being newly detected by antenatal screening. A number of cases of infectious syphilis are being diagnosed in this way. Routine quarterly reporting to the six PHLS reference laboratories, of all cases of treponemal infection, began in late 1994 and it is planned that reference laboratory reporting will form the basis of long term surveillance. The data from these surveys and laboratory reporting will form the basis of a policy analysis of the value of antenatal screening for syphilis which will be completed in late 1997.

References

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2 PHLS Communicable Disease Surveillance Centre. Sexually transmitted disease quarterly report; syphilis in England & Wales. CDR 1997; **7:** 192-4.

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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. In Europe it is estimated that 15% to 20% of babies born to HIV infected mothers, and not breast fed, are infected themselves, up to 25% of these develop AIDS within 12 months. The HIV infection status of the child can usually now be determined by 3 to 4 months of age.

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, 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 is reviewed yearly.

Analysis

By the end of January 1997 there had been 1115 reports through the BPSU. Six hundred and sixty-nine children born to HIV infected women, and therefore at risk of vertical transmission, were reported (see Table 6), together with 48 children who were infected in the course of treatment for haemophilia, 22 infected through blood transfusion, and two for whom the transmission route cannot be established. One hundred and sixty-two of the remaining reports were duplicates, and there were 189 reporting errors or cases where the paediatrician was unable to remember the child they had reported. Twenty-three reports are still being investigated.

A further 716 reported cases have been identified from other sources (see Endnote) including 463 children born to HIV infected women, 221 children with haemophilia, 17 infected through blood transfusion, and 15 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 summary tables appearing on a quarterly basis in the Communicable Disease Report (England, Wales and Northern Ireland) and ANSWER (Scotland).

Table 6 *Infants born to HIV infected women and confirmed cases of paediatric HIV infection (notified by 31 January 1997)*

Transmission route *(actual or potential)*	BPSU Reports	Reports from other sources	Total
risk of vertical transmission	669	463	**1132**
haemophilia treatment	48	221	**269**
blood transfusion/products	22	17	**39**
other/not yet established	2	15	**17**

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

HIV infection status	BPSU Reports	Reports from other sources	Total
AIDS	173	66	**239**
HIV infection (not AIDS)	111	70	**181**
indeterminate	134	211	**345**
uninfected	251	116	**367**
TOTAL	**669**	**463**	**1132**

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 HIV and STD Centre at CDSC. 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. Among the 1132 children born to HIV-infected mothers (see Table 7), 420 have confirmed infection, 345 are currently of indeterminate status and 367 are uninfected. Transmission rates cannot be estimated from these data as there is a bias towards the reporting of symptomatic children.

The majority of births to infected mothers are taking place in London. Comparison with the results of unlinked anonymous testing indicates that over 80% of maternal HIV infections remain undiagnosed at the time of birth. There are interventions that can greatly reduce the risk of mother to child transmission and it has been estimated that if all HIV-infected women attending for antenatal care in London consented to testing and took up interventions at the current rates, the number of vertically infected babies born in London each year could be reduced from over 40 to less than 15[1].

Uninfected children born to HIV infected women are not followed up routinely once they are known to be uninfected. However, with the increasing use of antiretroviral therapy to reduce mother to child transmission of infection, there is still a need for children exposed to such treatment perinatally to be monitored in order to ensure that any associated adverse outcomes occurring during childhood or adult life are recognised as quickly as possible. In collaboration with the Office of National Statistics we plan to monitor cancer and death registration in HIV-infected and uninfected, zidovudine-exposed and unexposed children, with appropriate safeguards to preserve anonymity and confidentiality.

The investigators would like to thank all members of the RCPCH, particularly those paediatricians who have reported cases and completed questionnaires.

Funding

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

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.

Reference

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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.

The BPSU included invasive *H.influenzae* infection occurring after Hib immunisation in its reporting scheme from September 1992 onwards and widened the case definition to include all children with invasive *H. influenzae*, regardless of vaccination status in November 1995. The surveillance mechanism has identified children in whom vaccination is unsuccessful, as worthy of further immunological evaluation and follow up as well as allowed preliminary estimates of vaccine efficacy to be made. The continuation of surveillance will address 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 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 vaccine status thus enabling:

i) estimation of the effectiveness of Hib conjugate vaccine in British and Irish children;
ii) determination of the importance of disease due to non type b *Haemophilus influenzae*
iii) 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 *Haemophilus influenzae* is isolated from a normally sterile site in a child under 16 years of age, irrespective of his/her vaccination status. A sample should then be sent to the PHLS National 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 PCR technique. When vaccine failure has occured attempts are made to collect acute and convalescent specimens of serum.

Case definition

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

Invasive Hi 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 fourfold rise in Hib antibody between acute and convalescent serum specimens is recorded.

Study duration

The study began in September 1992 and is reviewed annually.

Analysis

By April 1997, 412 reports had been made including 324 cases in vaccinated and 88 in unvaccinated children. Ninety-two cases represented true vaccine failures, 67 apparent vaccine failures and 11 were possible vaccine failures (possible vaccine failure is defined as, when protective course of vaccination received, isolate of *H. influenzae* obtained but not typed). Amongst vaccinated children there were 78 with invasive disease due to non capsulate strains of *H influenzae* and 21 with non b capsulate strains, mostly type f. Fifty-five reports did not meet the case definition.

Eighty-three of the 92 true vaccine failures were vaccinated in the first year of life: 73 received three doses and 10 received two doses. Nine 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 eleven months of age, 39 between 12 and 23 months of age, 18 between 24 and 35 months of age and three between 36 and 47 months of age. Surveillance has therefore allowed the following point estimates of vaccine efficacy to be made: 99.2% (95%CI 98.6-99.6) for children aged 5-11 months, 97.0% (95.8-98.0) for those aged 12-23 months, 95.6% (92.9-97.5) 24-35 months of age and 97.1% (92.7-99.2) for children between 36-47 months of age.

In the Republic of Ireland, numbers of cases in each age class together with point estimates of efficacy and 95% CI (assuming 75% uptake) are as follows: 8-11 months of age -1 (97.8%(87.9-99.9)), 12-23 months of age - 5 (92.7% (83.0-97.6)), 24-35 months - 2 (87.7%(55.7-98.5)) and 36-47 months of age - 0 (100%(24.7-100)).

The modes of presentation and associated medical and immunological conditions amongst the cases of true vaccine failure are detailed in Table 8. Overall 41 (45%) were shown to have an associated condition. There have been two deaths.

Convalescent sera were available in 86 cases of true vaccine failure. Twenty-seven (31%) demonstrated a poor antibody response to disease (<1 ug/ml), necessitating a booster dose of vaccine.

The majority of *H.influenzae* isolated from unvaccinated children have been non capsulate strains (43/88) with a predominance of neonatal disease, especially in premature infants. Hib has been isolated from 22 children, 14 (64%) old enough to have been fully vaccinated.

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 and comparable estimates of efficacy for HbOC (HibTITER), the conjugate vaccine used in the Republic of Ireland at a 2, 4, 6 month schedule. In the Republic of Ireland accurate vaccine coverage figures are not available and the relatively small population size results in wide confidence intervals. Should vaccine protection wane and given the absence of a booster dose in both countries, combined with the reduction in asymptomatic boosting by pharyngeal carriage of Hib (a theoretcial possibility), an excess of cases would become apparent in older children. Currently, point estimates of vaccine effectiveness remain very high up to and including the fourth year of life.

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 type b *H influenzae*. Measurement of convalescent Hib antibody levels following vaccine failure provides guidance on further doses of vaccine.

Following the impressive reduction in Hib disease 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 invasive 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.

The investigators continue to be most grateful for the collaboration of paediatricians, microbiologists and public health physicians in this study.

Table 8 *Presenting illness and associated conditions of true vaccine failures (TVF) Sept 1992 - April 1997*

Presenting Illness		Associated condition	
Meningitis	51	Prematurity	9
Epiglottitis	18	Cromosomal abnormality	4
Bacteremia	12	(includes 3 Down's syndrome)	
Cellulitis	5	Malignancy	4
Pneumonia	3	Dysmorphic	3
Septic arthritis	2	Cyclical neutropenia	1
		Immunoglobulin deficiency	27

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Medium chain acyl-CoA dehydrogenase deficiency

Background

Medium chain acyl-CoA dehydrogenase (MCAD) is an inborn error of fatty acid oxidation with a variable presentation. Some patients develop hypoketotic hypoglycaemia or an acute encephalopathy (similar to Reye's syndrome), whereas others may present with hypotonia, hepatic dysfunction, or they remain asymptomatic. The sudden and unexpected death of some cases may be attributed to sudden infant death syndrome. Studies of the frequency of the common mutation in heterozygotes suggest that MCAD deficiency is relatively common, with a birth prevalence of about one in 10,000. It seems, however, that the proportion diagnosed varies greatly, both internationally and from one region of the UK to another[1]. In many places less than 50% of the predicted cases are diagnosed clinically. Neonatal screening for MCAD deficiency by tandem mass-spectrometry is a feasible proposition and has been performed on over 80,000 babies in the USA [2].

Objectives

To identify all patients in the United Kingdom diagnosed during the period of the study. To provide data to inform decisions about whether to include MCAD in a neonatal screening programme. It is hoped that by increasing general awareness of the disorder the management of individual patients and their families will benefit.

Case definition

Through an accepted laboratory criterion. Data on genotype are also being collected.

Study duration

The study began in March 1994 and ended in March 1996.

Analysis

One hundred and three reports were received leading to the identification of 55 newly-diagnosed patients in 49 families. Most of the discrepancy between the number of returns and the number of patients was due to multiple reporting, reflecting the tendency for such patients to be referred on to specialist centres either prior to or following diagnosis. Further separate circulations was made to UK diagnostic laboratories in mid 1995 and late 1996 to confirm the validity of the returned data. These circulations have so far produced a further seven cases in five families. An additional case, whose family was serving in the US Air Force was discounted, as was a child whose family was stationed abroad with UK Armed Forces and who was diagnosed in Germany.

In 15 of the cases there was a family history. Seven of the new cases were babies born into families where MCAD deficiency had been diagnosed in an older sib. They were diagnosed in the neonatal period as was a further baby who was investigated because an older sib had died of "Reye's syndrome". In three families an older sib, in one a twin, and in one two younger sibs of newly-diagnosed cases of MCAD deficiency were also diagnosed to have the condition, though as yet they had shown no clear symptoms. A further child, born into a family known to be at risk, was erroneously diagnosed as unaffected shortly after birth but then had a hypoglycaemic episode at one year of age.

The age at diagnosis in the index cases ranged from two days (fortuitously in the course of another investigation) to twelve years. In four cases an episode occurred in the first week of life, one case proving fatal. Overall, ten patients died following an acute illness. Six surviving patients show some degree of neurological impairment. Despite the apparently good diagnostic performance in the UK, with 80% of symptomatic patients diagnosed after only one episode, there is clearly still substantial morbidity and mortality, with a death either definitely or probably attributable to MCAD deficiency in 16 of the 54 affected families.

Further work

The findings of this survey are being prepared for publication. Preliminary data have been incorporated into the economic model of a recent Health Technology Assessment of neonatal screening for the NHS Research & Development programme[3].

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Neonatal meningitis

Background

Ten years ago 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 countrywide 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 streptococcus, *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 had 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 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, morbidity, 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 we first surveyed ten 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 were treated as neonatal meningitis by the paediatrician should be included. Cases of viral meningitis should be included. Babies where meningitis was diagnosed at autopsy should be included. Cases with neural tube defects should be excluded.

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

The investigators would be pleased if BPSU respondents could report all babies meeting these criteria. Confidentiality will of course be preserved at all times.

Study duration

July 1996 - July 1997, further extension subject to review.

Interim results

The results given here include all those received up to 17 April 1997.

The Karim Centre has received 221 notifications of neonatal meningitis from the BPSU. Of these, 29 are known to be either initial errors in reporting, ie. there was no meningitis, the child was too old or the onset of the disease was before the study start date, or the same case had been reported by more than one paediatrician.

Of the 192 questionnaires sent out to paediatricians, 93 replies have been received, a 48% completion rate. Of the 93 questionnaires subsequently sent to microbiologists, 65 replies have been received, a 70% report rate.

Bacterial meningitis predominates (41/93, 44.1%), with only six cases of confirmed viral meningitis reported (6.5%). The remainder were CSF culture negative but with white cells raised (40/93, 43%), or clinical evidence only (4/93, 4.3%). There was one case of candida infection and one case remains unconfirmed.

Of the 41 cases where bacteria were isolated from the CSF, 21(43.8%) were Group B streptococci, 7(14.6%) were *Escherichia coli*, 3(6.3%) were Listeria and the others were single incidences from a range of bacteria. The antibiotic commonly used in treatment were cefotaxime, gentamicin, penicillin and ampicillin.

At the time of completion of the form by the paediatricians, 14 (15.1%) of children remained in hospital, 65 (69.9%) had been discharged, 13 (14%) had died and one diagnosis was made postmortem.

Of the 63 reporting laboratories, 18 had carried out virus culture while 24 had used one or more methods for detection of the organism in addition to culture. These methods included counter immunoelectrophoresis, latex agglutination, enzyme linked immunosorbent assay and polymerase chain reaction.

Comments

While it is too early to draw any conclusions from these data, it is useful to make one comment. It is clear that in the cases which have been reported in detail to us lumbar puncture predominates as a means of diagnosis. Only in two cases have CSF samples not been obtained, one where it proved impossible to do so on more than one occasion and the other where the diagnosis was made at autopsy. The investigators are very grateful for all the completed questionnaires and would encourage the return of of any questionnaires outstanding.

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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 published literature, all in case reports or small hospital based series. No large scale or population based study has ever been reported. The incidence and prevalence are 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. The condition may 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 dose of pyridoxine required for individual patients varies between 10 and 1000mg 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:

a) determine the prevalence of definite or possible pyridoxine dependent seizures in children under 16 years of age

b) prospectively study the incidence in children under five years of age.

c) 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 are 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 100mg, minimum 50 mg), that recur when pyridoxine supplementation is withdrawn, and that cease again when pyridoxine is given as above.

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

Reporters are asked to include cases in whom there are other suspected or definite causes of seizures, to ensure complete reporting.

Study duration

September 1995 - October 1997

Anaylsis

Forty two notifications have been received. This excludes six informal notifications and seven cases previously studied in the Northern Region but as yet unreported to the BPSU. Thirty questionnaires have been returned: of these, eight did not fulfil the criteria and four were duplicates.

The remaining eighteen have seizures that are pyridoxine dependent to varying degrees of certainty. Four are 'definite', as proved by formal trials of withdrawal. The others are not proved to be dependent, but are still under treatment. This includes two with infantile spasms. One other child not included in the above had steroid resistant infantile spasms that were controlled by pyridoxine, but has now stopped treatment without relapse. Pyridoxine appears to have some anti-convulsant effect. Other cases have been reported who do not have classical pyridoxine dependency in that the response to pyridoxine was incomplete or seizures did not recur after pyridoxine withdrawal.

Three children have been born during the study. In total six of the eighteen were aged less that one year at notification. The other twelve have a random scatter of ages. This could be due to review of the diagnosis reducing the number of older children, under-referral of old cases, or an increased diagnostic pickup in the last two years. Some children may be seen in follow up clinics by staff who do not receive the orange card. This will lead to missed cases and could contribute to a reduced number of old cases being notified.

Nine of the eighteen have come from the North West and Mersey regions. If the Northern regional cases are considered this suggests a northern preponderance, but there is only one case from Scotland. Four more have come from the four Thames regions, mostly from outside Greater London, and one each from five other regions. This regional variation is unexplained.

Certain notification have been impossible to follow up because there is no record of the child's name. Some of these were by locums who then left the hospital without leaving a record for their successor. There seems to be delay of about four to eight weeks between notification and receipt of the questionnaire, which tests some of the best memories! This emphasises the importance of recording the identity of the other half of the orange card. Problems have also occurred with children from certain ethnic groups where the 'surname' of a baby is changed after birth. Thus it might be worth recording their hospital number as well. These difficulties could be prevented by trying to speed up the response by the investigator, perhaps by telephoning the referring paediatrician's secretary on receipt of the notification.

Conclusions

Pyridoxine dependent seizures have a low birth incidence. There are unexplained variations in the distribution of this condition according to age and geographic origin. Pyridoxine responsive seizures, including infantile spasms, also occur in young children.

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Reye's syndrome

Background

Surveillance of Reye's 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's syndrome in the British Isles was similar to that in the United States 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's syndrome and consumption of aspirin. In response to this and similar findings in the United States, 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's 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's 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 case definition is relatively non-specific, cases reported from surveillance year (see Table 9) 1994/5 onwards, whose diagnosis has not been revised, have been allocated a "Reye-score"[1].

Study duration

The BPSU involvement with this study began in June 1986; it has been granted a further one year extension to July 1998.

Analysis

Between August 1981 and July 1996 a total of 598 suspected cases of Reye's syndrome were reported to the surveillance unit (Table 9), but the diagnosis was subsequently revised in 148 cases (25%). Nearly half (47%) of the revisions were to one of the 'Reye-like' inherited metabolic disorders. In the year to July 1996, 18 reports of new cases were received and follow up was complete on 17 of these at time of writing. Two of the 17 diagnoses had subsequently been revised, leaving 15 cases whose clinical and pathological features were compatible with Reye's syndrome. All cases except one were reported via the BPSU. One patient was ascertained via a death entry alone. This was an 11 year old male who died suddenly at home.

One further case was ascertained via death entry in 1995/6. This was a 14 year old male who had an illness diagnosed as Reye's syndrome in 1982 at age 5 months; he was not reported to the surveillance scheme at the time. He was left with severe neurological damage and died from bronchopneumonia in 1996.

Cases compatible with a diagnosis of Reye's syndrome (N=15): year to July 1996

There were eight males and seven females; the ages ranged between three months and 15 years with a median of 38 months. Ten lived in England, three in Scotland and two in the Republic of Ireland. Four were ill between August and November; eight had their onsets between December and March, and three between April and July. All of the eight survivors were reported to have made a full recovery with no neurological sequelae. Of thirteen patients with information on preadmission medication, four had received none; three had received paracetamol alone; two had been given paracetamol and aspirin; one had had aspirin alone; another, aspirin plus inderal; one, an antibiotic and one, a benzodiazepine.

Two patients were reported to have had no prodromal illness; nine had had upper respiratory tract or 'flu-like symptoms; two had vomiting and diarrhoea and two had had non-specific preadmission symptoms - lethargy with pallor and headache with photophobia. A rotavirus was recovered from faeces in one patient, an adenovirus from the nasopharynx of another, and in one patient there was serological evidence of influenza A infection; none of the others had microbiological confirmation of infection. Eleven patients were reported to have been investigated for inherited metabolic disorders; four (aged three

months, 27 months, 39 months and 11years) had not. The 'Reye Score' (possible range, 1-25) ranged between 6 and 17 with a median of 12 and mean of 12.5.

Revised diagnosis cases (N=2):

One, who survived, was a 14 month old female found susequently to have medium chain acyl coA dehydrogenase deficiency. The other, who died, was a nine year old male already on sodium valproate before admission, in whom the liver histology showed not only Reye-like fatty infiltration, but also numerous eosinophils. It was considered that his illness was a drug induced hypersensitivity reaction.

Comment

Two of the trends observed in 1994/95 continued in 1995/96, namely the persisting low annual total reports compared to those seen in the 1980s, and the declining proportion (12% compared with 21% in 1994/95) of cases in whom the diagnosis is later revised. The latter trend is expected as it probably reflects increasing awareness of 'Reye-like' inherited metabolic disorders. In keeping with this, nearly three quarters of the patients were reported to have been investigated for those conditions, a similar proportion to last year.

Although details of the investigations are not sought on our questionnaire, (so the rigorousness with which an inherited metabolic disorder has been excluded as the cause of the child's illness is unknown), they were volunteered by the reporting clinician in three cases: a male aged 13 years an two females aged 12 months and 19 months. These patient are of interest because all were atypical for 'classic' Reye' syndrome (the boy because of presentation as sudde unexpected death and the girls because of their young age an some unusual biochemical and histological features), ye extensive investigation at centres of excellence for inherite metabolic disorders did not yield an alternative diagnosis.

These cases illustrate the difficulty in diagnosing 'classic' Reye' syndrome, because the case definition is so non-specific an because there may still be 'Reye-like' inherited metaboli disorders as yet undiscovered. Thus, unlike many other condition surveyed by the BPSU, a case of 'Reye's syndrome' can rarel if ever, be described as 'confirmed'. Cases are better designate as 'compatible with' the diagnosis.

Although the proportion of cases investigated for an inherite metabolic disorder was encouraging, there is nevertheless sti cause for concern. It was unchanged from last year and fou patients (27%) including three who, by virtue of their youn age, should have aroused diagnostic suspicion, were nc investigated. Furthermore, the preliminary findings of th follow up study of seven cases between 1993 and 199 ascertained by death entry only (mentioned in last year' report) suggest that in only two were investigations for a inherited metabolic disorder undertaken. All presented a sudden unexpected death, six were aged two years or unde and the diagnosis of Reye's syndrome was made solely on th

Table 9 *Reye's Syndrome Surveillance 1981/82 - 1995/96*

Reporting period (August-July)	Total reports from the British Isles	Revised diagnosis (inherited metabolic disorder in brackets)		Cases of Reye's 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
TOTAL	598	148	(70)	432	226

1 *Follow up not received for one case*
2 *Follow up not received for two cases*
3 *Follow up not received for four cases and one case did not meet the case definition*
4 *Follow up not received for five cases*
5 *Follow up not received for three cases*

* *Compatible with the diagnosis (see text)*

basis of the macroscopic or microscopic appearance of the liver. There is clear need for continuing education of both clinicians and pathologists in the recognition and diagnosis of Reye-like inherited metabolic disorders, many of which may present as sudden death.

There were a number of epidemiological features of reported cases in 1995/96 which differed from previous years; the median age, case fatality rate and number and proportion reporting pre-admission aspirin exposure.

The median age, 3 years 2 months, was the highest since surveillance began: in the 1980s it was around 14 months and this fell to 10 months in the early nineties, though it rose again to 14 months last year. Seven of the 15 1995/96 cases were over 5 years, a more typical age for 'classic' Reye's syndrome than younger children. Their mean Reye score was 14.1 (compared to 12.5 among the cases as a whole) and all four who had taken aspirin (mean score 15.8) were in this group. The three patients who had not taken aspirin (mean score 12.0) all manifested some unusual clinical and pathological features, including two who presented with sudden unexpected death.

There were seven deaths in 1995/96, the highest number since 1989/90. All seven had atypical clinical and/or pathological features.

The number (four) and proportion (30% of those with information on preadmission medication) of cases reporting pre-admission aspirin exposure was the highest since 1986/7, the year of the public and professional warnings about the use of aspirin in children under 12. It is also noteworthy that, of the total 14 aspirin associated cases since 1986/87, six have been over the age of 12 years. This compares with eight of 34 such cases between 1984/85 and 1985/86. These data suggest that there may be a need both for a renewed public and professional education campaign and for reconsideration of the justification for 12 years as the upper age limit on the warning. In the United States such labels are required to refer to 'children and teenagers'.

The investigators thank all BPSU respondents who have kindly reported cases, completed proformas and sent further information.

Funding

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

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Subacute sclerosing panencephalitis

Background

The register of cases of 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 Disease Surveillance Centre (CDSC). In 1989 responsibility was transferred within CDSC to Dr Norman Begg and in 1993, to Dr E 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.

The number of cases arising since 1982 has fallen following about 10 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.

SSPE has been included in the BPSU reporting system since it began in 1986. It came off the card in October 1994 and was placed back on in September 1995 as no new cases had been reported since its removal a year earlier and it was necessary to know if this was a true reflection of incidence.

Objective

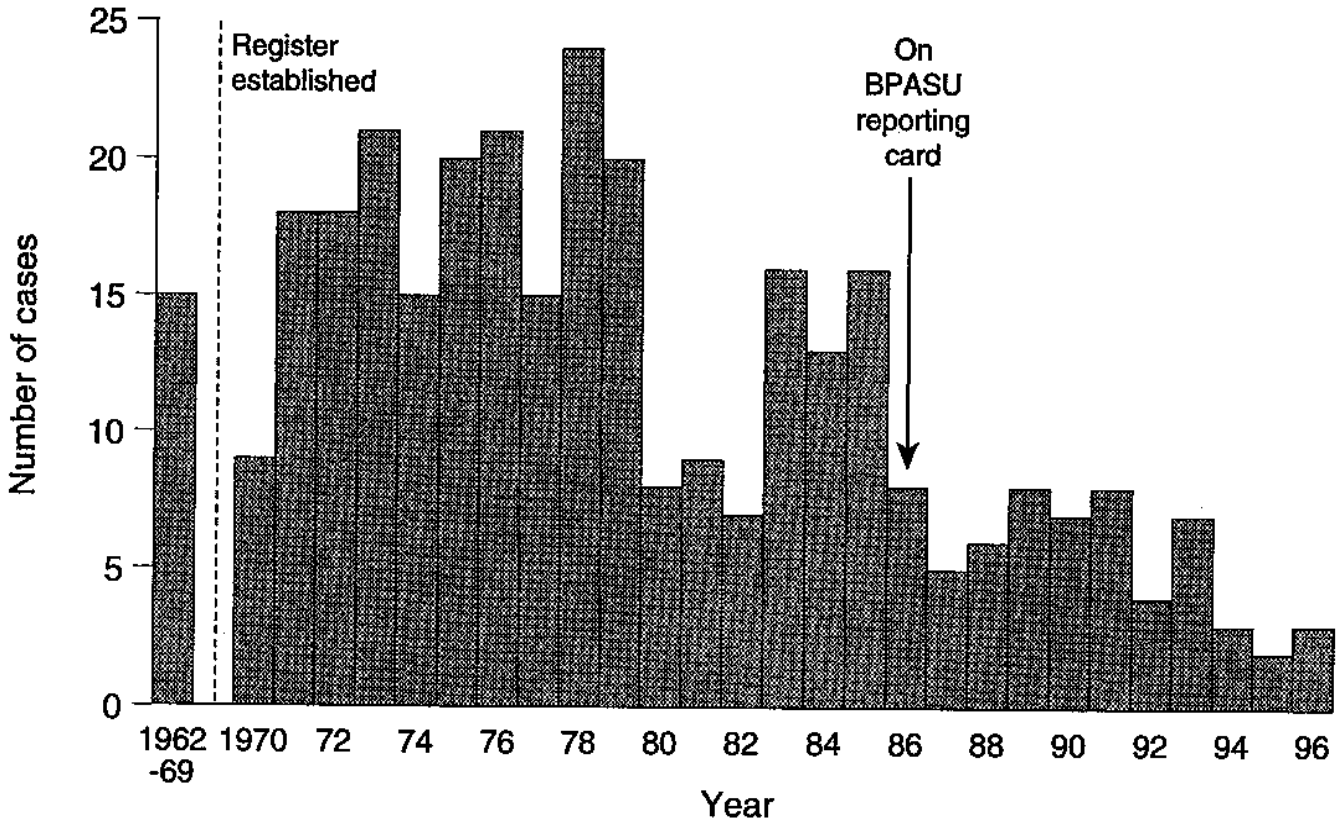
To monitor the incidence of SSPE.

Case definition

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

i) Raised measles antibody titres in the serum and CSF indicative of intrathecal antibody production and a higher level in the CSF compared to serum.

Figure 3 Cases of SSPE in England and Wales by year of onset 1962–1996



Prepared by CDSC

ii) Typical EEG changes

Iii) Typical brain histology or other evidene of measles virus in brain tissue

A definitive case requires the prescence of i) and ii).

Study duration

The study began in June 1986, following passive reporting to Communicable Disease Surveillance Centre (CDSC). Between July 1994 and October 1995 passive surveillance was undertaken from CDSC.

Results

Since 1995 surveillance has once again been undertaken through the BPSU. This was approximately one year after the national measles-rubella (MR) vaccination campaign in which over 7 million children aged 5-16 years received a dose of MR vaccine during November 1994. The MR campaign had significance for SSPE surveillance for two reasons. Firstly, it eliminated endemic transmission of measles in the UK and thereby should have ensured the elimination, in the longer term, of UK acquired SSPE. Secondly, one case of SSPE was reported on a 'Yellow Card' to the Committee of Safety of Medicines as a possible reaction to MR vaccine. Although the case had a history of wild measles infection during childhood, it nevertheless raised concerns in some quarters that exposure to measles vaccine might act as a trigger for the onset of SSPE.

The number of confirmed cases ascertained through the BPSU, and other sources such as death certificates, since 1985 is shown in Figure 3 according to year of onset. There is no evidence of an increase in cases since the MR campaign. Of the 42 cases ascertained since 1989, 10 (24%) were Asian, confirming the increased risk in this ethnic group. Six of the 42 children were immigrants from countries with a high measles incidence and are therefore unlikely to have acquired infection in the UK.

A history of measles vaccine and/or vaccine has so far been obtained for 38 children; of these only seven had no history of measles disease of whom three had a documented history of measles vaccination. The proportion of children without a history of measles who were vaccinated (42%) is consistent with that expected by chance given UK vaccine coverage figures and assuming that subclinical measles during the first year of life is responsible for SSPE in children without a history

of measles. A definitive anlaysis will be done when the data on prior measles disease and vaccination are complete, but the results so far do not suggest that SSPE is caused by vaccine. The protective effects of vaccination on SSPE rates in the population are now becoming evident following the decline in the incidence of acute measles achieved since the introduction of MMR in 1988. Excluding imported cases, the mean annual number of SSPE cases with onset in the period 1993-6 was three; this compares with an annual number of between 15 and 20 in the 1970s. The median age of the twelve UK acquired cases with onset between 1993-6 was 11 years, consistent with these being the residual cases with longer incubation periods following measles acquired during the 1980s.

Conclusions

1 The benefits of the MMR programme on preventing SSPE are now emerging.

2 Epidemiological evidence to date suggests that in the small number of vaccinated cases without a history of clinical measles, SSPE was not vaccine-induced.

3 With the elimination of endemic measles transmission in the UK, the elimination of SSPE within the next decade can be expected.

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6 New studies for 1997

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 main recommendations was that a national prospective surveillance study of haemolytic uraemic syndrome (HUS) should be set up.

HUS is a heterogeneous condition characterised by microangiopathic haemolytic anaemia (fragmented red blood cells), thrombocytopaenia and acute renal impairment[4,5]. HUS has a number of aetiologies and the most important is Vero cytotoxin-producing *E. coli* O157 (O157 VTEC)[1,7,8,9,10]. VTEC of several other serogroups have also been associated with cases of HUS[1,7]. Two 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 settings[1]. 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 and humans become infected through the consumption of contaminated foods, particularly minced beef and milk[1,2,3,11]. Outbreaks of VTEC infection including cases of HUS have been associated with a range of vehicles other than beefburgers and milk, such as yogurt, 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 both in families and institutional settings[1].

The BPSU survey of 1986-1989 found an incidence approaching two per 100,000 child population per annum. Reports of VTEC 0157 infections have risen since then; eight cases were confirmed by laboratories in the UK in 1988 and 1156 in 1996. The new study will explore effect of this increase in the VTEC 0157 on the epidemiology of HUS.

Study duration

Start February 1997. For three years with annual reviews.

Coverage

United Kingdom and the Republic of Ireland.

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>8mmol/l);

2 Microangiopathic haemolytic anaemia (Hb <10G/l with fragmented red cells);

3 Thrombocytopaenia (platelets < 130,000 x 10^9/l).

The above may not all be present simultaneously.

In the absence of

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

Methodology

1 **Local hospital:** Paediatricians have been asked to report to the BPSU suspect and definite cases of HUS. When required, guidance on diagnosis will 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 and in Scotland to SCIEH. 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 CDSC or SCIEH 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 will advise on clinical aspects of the study on behalf of the British Association for Paediatric Nephrology.

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**References (1-10) available from researcher 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%). The other 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 is lacking. Viral inactivation of clotting factor concentrate started 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 specialties may be involved in the management and follow up of children who have been identified.

Study duration

March 1997 - March 1998 (13 months)

Coverage

UK and Republic of Ireland.

Objectives

1 To estimate the prevalence and distribution of known paediatric HCV infection in the UK and Eire;
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.

Methods

Reporting paediatricians will be 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.

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

Progressive and intellectual neurological deterioration

Background

The recent appearance of **new variant CJD (nvCJD)** in patients as young as age 16[1] has raised the question as to whether the condition is occurring in children. 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. As the presentation of nvCJD in adults is not typical of classical CJD[1], 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. The group needs to be large enough to include all possible cases of CJD, hence surveillance is being undertaken for a range of presentations under a combined term **Progressive Intellectual and Neurological Deterioration** (PIND).

Study duration

May 1997 to April 2000

Coverage

United Kingdom only

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 will be evaluated critically in order to classify them and investigate the possibility that Creutzfeldt-Jakob Disease (CJD) 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 :

1 Progressive deterioration for more than three months
with
2 Loss of already attained intellectual/developmental abilities
and
3 Development of abnormal neurological signs.

Excluding:
Static intellectual loss e.g. 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).

Methods

Paediatricians reporting a child who presents with PIND will be sent an initial short (one page) contact form and asked to provide a telephone number (and fax number if available). They will then be contacted by the research nurse or research administrator to arrange a more detailed telephone discussion to gather further information. Thereafter, the research nurse may request a visit to the reporting paediatrician to review the case notes and discuss the case further. The PIND Research Group will not expect the referring paediatrician to discuss the notification of PIND with the child's family. The aim of the PIND Research Group is to classify all cases of PIND and to identify any child with clinical features suggestive of CJD. If such a child is identified, the PIND Research Group will discuss that child with the referring paediatrician. If the referring paediatrician is in agreement, the child with suspected CJD will then be notified to the National CJD Surveillance Unit. Throughout, all patient data will be dealt with in strict confidence and the paediatrician managing the case will remain in control of patient referral. The PIND Research Group will not be contacting families directly.

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7 Past studies revisited

Congenital dislocation of the hip

Background

A national policy of universal neonatal screening for congenital dislocation of the hip (CDH), based on clinical examination and risk assessment in newborn and very young infants, was formally introduced in 1969.[1] While the principal objective was to ensure a functionally and radiologically normal hip at the end of the period of adolescent growth, a reduction in the number of children requiring at least one operation for CDH had been anticipated.

Subsequently, there has been controversy as to whether this programme is effective. The perceived failures of the current screening policy, together with implementation of universal primary ultrasound screening in some European countries, have generated interest in the use of ultrasound imaging of the neonatal hip as a primary screening test in the UK. However the effectiveness of this strategy has not been established, and there has been concern that, in countries operating a policy of universal screening with ultrasound, rates of non-surgical treatment are up to 17 times higher than in the UK, with up to 16% of all infants born requiring follow up for initially ambiguous ultrasound appearances.

As national data were lacking from which to estimate the 'size of the problem', specifically, the extent to which children were not being detected by the current screening programme, a national surveillance study, commissioned by the UK Medical Research Council (MRC), was carried out in collaboration with the British Paediatric Surveillance Unit (BPSU) and the British Orthopaedic Association (BOA). A parallel national survey to establish current screening and management practices was undertaken.[2] This survey identified increasing use of ultrasound imaging to assess infants with clinically detected hip instability, but virtually no primary screening with ultrasound within the UK.

Objective

To determine the incidence of treatment for hip dislocation or instability with abduction splinting or an operative procedure in children aged 5 and under in the UK.

Case definition

i) Infants and young children aged 5 and under receiving a first operative procedure for CDH, with or without general anaesthesia;
ii) Infants receiving initial treatment with abduction splinting.

Sources of data

British Paediatric Surveillance Unit and Orthopaedic Surveillance Scheme - Cases of abduction splinting were ascertained through the BPSU and a parallel Orthopaedic Surveillance (OS) scheme among surgeons established specifically for the MRC study in collaboration with the BOA.[3,4] The surgeons were also asked to report cases of a first operative procedure. Duplicate reporting was minimised within larger centres by arranging for a single clinician to be responsible for reporting all cases.

Routine data - Hospital Episode System (HES) data were used as a second source of data for children receiving an operative procedure, and cases ascertained through this source were verified by inspection of hospital medical records in Scotland, Wessex and the Northern regions, areas which together account for than 18% of UK births. Capture-recapture analysis was used to produce ascertainment-adjusted estimates of the prevalence of first operative procedures. A similar approach for estimates of abduction splinting was not possible, since a second reliable data source meeting the conditions necessary for capture-recapture analysis was not available.

Study duration

Active reporting began in April 1993. Reports of cases of abduction splinting were requested for four months, and cases of a first operative procedure for thirteen months.

Results

Abduction splinting - For the initial 4 month period of reporting, the card return rate for paediatricians was 91%, and that for orthopaedic surgeons, 83%. Questionnaires were returned for 684 (72%) of 944 cases of abduction splinting notified (346 by paediatricians and 598 by orthopaedic surgeons). Of the questionnaires returned, 150 cases were ineligible (mainly because treatment had been initiated outside the study period) and 71 were duplicates. From these data, the incidence (95% Confidence Interval [CI]) of abduction splinting in the UK is estimated to be 1.6 (1.4 to 1.7) per 1000 live births. By including all notified but unconfirmed cases as true cases, a revised estimate (95% CI) of 2.4 (2.3 to 2.6) per 1000 live births is obtained.

Operative procedures - Questionnaires were returned for 436 (78%) of the 556 cases of a first operative procedure notified by orthopaedic surgeons. Of these, 103 were ineligible (mainly because the date of the first procedure was outside the study period), and 14 were duplicate reports. This gives an unadjusted estimate (95% CI) of 0.39 (0.34 to 0.43) first operative procedures per 1000 live births. Case ascertainment using two sources (OS scheme and HES data) was estimated to be 90% complete in the validation regions. Using capture-recapture analysis, an ascertainment-adjusted prevalence (95% CI) of a first operative

procedure for the UK was estimated to be 0.78 (0.72 to 0.84) per 1000 live births. Two thirds of children receiving a first operative procedure had not been detected by screening, of whom half were detected as a result of parental concern alone. One third of those not detected by screening had at least one recognised risk factor for CDH.[4]

Comment

The prevalence of a first operative procedure for CDH in young children is similar to that in unscreened Northern European populations, which has been reported to range from 0.8 to 1.6 per 1000 live births. In the current study, a significant proportion of children requiring at least one operative procedure for CDH were not detected by screening and were initially ascertained through parental concern.[4]

The prevalence of abduction splinting in the UK is higher than the rate of CDH in Northern European unscreened populations.While individual centres have previously reported higher rates of abduction splinting, there has been a tendency for these to fall with time, which may reflect changing patterns of referral and management of screen positive neonates.[2]

Existing evidence does not support the introduction of universal primary screening with ultrasound in the UK and further evaluation is required. Using information provided by the MRC national survey and surveillance study, a multicentre randomised trial has been established to evaluate the use of ultrasound imaging in the management of infants with clinical hip instability. This trial - the 'Hip Trial' - is in progress and is co-ordinated by the Perinatal Trials Service in Oxford. Clinical outcome, based on radiological evaluation at two years of age, as well as economic and psychosocial outcomes, will be compared in infants managed with ultrasound and those managed conventionally. Evaluation of this use of ultrasound was given priority because it was being increasingly adopted as part of routine practice in the UK and the evidence to support it was not strong.

Strong evidence to support the effectiveness of primary clinical screening for CDH is lacking and the objective of the MRC review is to help develop a more scientific basis for screening policy. The sensitivity of clinical screening may be low, but there is, as yet, no convincing evidence to show that primary ultrasound screening performs any better. A cost-effectiveness analysis of current and alternative screening strategies will commence in September 1997 as the next stage in the MRC review. The objective of this analysis is to help prioritise and, if appropriate, plan a randomised trial of primary screening for CDH.

Funding

This work was funded by the UK Medical Research Council. Dr C Dezateux was funded by the Wellcome Trust.

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Neonatal herpes simplex infection

Background

Neonatal herpes simplex virus (HSV) infection is a serious condition with a high mortality rate and considerable morbidity among the survivors. Infection is usually acquired at the time of delivery during passage through an infected birth canal, or by ascending infection after rupture of the membranes.

During the 1980s the number of cases of genital herpes appeared to be increasing in the UK and there was concern about the management of genital herpes infection in pregnancy. In the USA, where the incidence of neonatal infection was reported as 20-50/100,000, recommendations favoured weekly virus cultures in the last six weeks of pregnancy for women with a history of genital herpes, and delivery by caesarean section for those shedding virus close to term. There was little information about the incidence of neonatal herpes in the UK, which was rarely reported and policy and practice of managing HSV infected pregnant women varied considerably across different parts of the country.

Study duration

1986 - 1991

Objectives

Primary: To estimate the incidence of diagnosed herpes simplex virus (HSV) infection in neonates in the British Isles.

Secondary: To ascertain the clinical manifestations of neonatal HSV infection and its long term sequelae.

Case definition

Any infant under one month of age with a diagnosis of HSV infection based on virus isolation.

Analysis

There were 137 notifications of suspected neonatal HSV infection in infants born between July 1986 and December 1991. Sixty-one cases were confirmed by virus isolation, and in another five a confident clinical diagnosis of neonatal HSV infection was accompanied by seroconversion in the infant or serconversion in the mother around the time of delivery, as well as compatable histological findings. Ten additional cases were classified as compatable cases on the basis of clinical signs of infection alone. The 61 remaining notifications were excluded: five of these were possible cases which did not satisfy the case definition; eight, the paediatrician was unable to identify the infant notified and the remainder were duplicates or reported in error.

Over a five and a half year period (1986-91), 76 infants with neonatal HSV infection were reported (including ten compatible cases). This gives a minimum incidence of recognised infection in the British Isles of 1.65/100,000 live births [95% CI 1.3-2.0].

Hence between seven and 18 infants with confirmed infection were born annually and between one and three with features compatible with HSV infection. There were no clear seasonal or regional patterns.

Twenty-five of the 76 infants had HSV-1 infection, 24 HSV-2 and in 27 virus type was unknown. Twenty-seven had disseminated infection, 23 herpes encephalitis and 26 localised infection. Nineteen infants (25%) died in the neonatal period, and a further 25 (33%) have subsequently died or have long-term sequelae. At least half of the infants had been discharged home before symptoms became apparent. For 21 women there was evidence of a maternal genital herpes infection at some time, but this was reported or diagnosed retrospectively after neonatal HSV was suspected in 19 cases, and antenatally in only two.

Conclusions

Neonatal HSV is rare in the British Isles and routine antenatal screening for genital herpes infection during pregnancy is not justified although caesarean section for women with clinical signs of genital infection at term is advisable. A high proportion of infected infants present with non-specific signs and symptoms and without mucocutaneous involvement; furthermore, there is rarely a history of maternal infection. As early diagnosis and prompt treatment is essential, there must be a high level of awareness of the serious nature of neonatal HSV infection.

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Neonatal necrotising enterocolitis

Background

Necrotising enterocolitis is a serious gastrointestinal disease seen principally in neonatal intensive care units. The reported mortality in established cases is between 20% and 40%.

No single aetiological factor seems to explain neonatal necrotising enterocolitis; its mucosal lesion can be provoked in several ways. It is important therefore to determine whether risk factors exist which can be avoided readily in clinical practice. Feeding policy is one such amenable factor. A recent prospective study carried out in five centres suggested that breast milk protects babies born prematurely from necrotising enterocolitis[1]. In babies fed exclusively with formula milk the incidence of confirmed disease was six to ten times greater than those fed breast milk alone, and three times greater than in those who received formula plus breast milk. Pasteurised breast milk seemed to be as protective as raw breast milk.

From this data and crude estimates of the proportion of premature babies who receive no breast milk in neonatal care, it is thought that many cases of necrotising enterocolitis occuring in Britain each year could be attributed to exclusive formula feeding.

Objective

This study was introduced to establish the incidence of necrotising enterocolitis and to determine whether early diet can influence its onset and severity.

Case definition

Grade 1

Cases have at least two of the following features: pneumatosis intestinalis seen on abdominal radiograph; abdominal distension, or an abdominal radiograph that shows gaseous distension or frothy appearance of bowel lumen (or both); blood in the stool; lethargy, hypotonia, or apnoeic episodes, or a combination of all three.

Grade 2

Cases have, as well as features of Grade 1, one or more of: abdominal bleeding in response to trauma; tenderness or rigidity; mucosal tissue in the stool; abnormal bleeding in response to trauma, or spontaneous bleeding; peripheral white blood cell count below 6 x 10^9/l at the time of illness; peripheral platelet count below 100 x 10^9/l at the time of illness; or an abdominal radiograph that shows gas in the portal vein or free air in the abdomen.

Study duration

This study began in October 1993 and ended in October 1994.

Analysis

Four hundred and twenty nine cases were reported during the twelve months of the study. Fifty-two of the cases were duplicate reportings, 28 were reported outside the twelve months in question, 21 were reconsidered not to be true cases of NEC, 28 cases were 'lost cases' - where identification details of the case had not been retained .

Therefore out of the 429 reported, 300 actual cases remain that fulfilled criteria for Grade I or II disease. Cases were confirmed if one of the following criteria was met: gas in the bowel wall or portal tract, diagnosis confirmed at surgery, diagnosis confirmed at autopsy. 185 out of the 300 were thus confirmed as cases by this more stringent criteria and 115 were suspected. Confirmed cases of NEC had a significantly higher proportion of grade 2 disease than suspected cases: 78% (145/185) versus 37% (42/115). Overall 52% of reported cases were male and 48% female.

A retrospective survey was also undertaken being sent to 262 NICU's and SCBU's, 109 replied reporting 197 cases of NEC. The second survey helped with validate the total number of case reported (see discussion).

The range of birthweight for all cases was 460-4870g, with 65% of all cases under 1500g. NEC was found to be most severe in those infants with the lowest birthweight and lower gestation. Fifty-four percent of all cases were less than 30 weeks gestation and 12% were 37 weeks or older (i.e. term). There was a significant negative correlation with gestational age and day of onset of NEC ($R=0.47$, $P<0.001$), whether the disease was confirmed or not.

The most common presenting clinical features for confirmed cases were abdominal distension (77% - 86% in suspected cases), lethargy, hypotonia, or apnoea (64% - 71% in suspected cases), abdominal tenderness (58%), pneumatosis intestinalis (57% - 5% in suspected cases), and blood in stool (39%).

Ninety one cases representing 30% of all NEC cases (n=300) and 49% of confirmed cases (n=185) received surgical management. Surgical intervention for full term infants was under half that in preterm infants.

Overall mortality rate was 22% (65/300). Mortality rates for confirmed cases were significantly higher than that for suspected cases. It was also found that as birthweight or gestation increased, mortality was reduced whether NEC was confirmed or not.

Feeding practices differed between gestational groups. Those under 30 weeks gestation received at least some human milk compared to infants who were 30 weeks gestation or over.

Those fed predominately on human milk were significantly less likely to develop confirmed disease, than those predominately on formulae milk.

Mortality rates between those fed predominately on human milk versus predominately formula did not differ. Although those above 30 weeks had a significant lower mortality if fed predominately human-milk.

Discussion

This is only the second study in the United Kingdom with over 100 cases of NEC, and has permitted a detailed description of the clinical epidemiology of the disease. The study provides further support for the protective role of breast milk in the development of NEC, with reduced disease severity in the human milk-fed group.

The estimated incidence of confirmed NEC was 0.23 per 1000 live births, increasing to 2.1 per 1000 neonatal unit admissions. These figures are probably an underestimate since probably not every case of NEC was reported. This was confirmed through the retrospective survey of NICU's and SCBU's. It is estimated that about 58 additional cases should have been reported, along with the estimate that 90% of the 28 cases reported but where no clinical data was available were NEC - bringing the total to 384, a 28% increase. Taking this figure, and assuming the same proportion of confirmed cases , the estimated incidence of confirmed NEC would rise to 0.30 per 1000 live births and 2.7 per 1000 NICU admissions.

Mortality rates for all reported NEC were 22%, increasing to 28% for cases of confirmed disease. Age of onset was significantly correlated with gestation, demonstrating that the late onset of NEC was more common in the infants with low gestation and vice versa. Perhaps this could relate to the earlier use of enteral feeds at higher gestation. As expected, mortality was higher in infants with very low birthweight and with more severe disease; in babies under 750g with grade 2 disease, mortality was 50%.

Human milk intake was associated with reduced severity of disease. Amongst all infants who had evidence of NEC, irrespective of gestation, those fed predominately on human milk were significantly less likely to have confirmed disease than those fed predominately formula. Since infants with confirmed disease were more likely to require major surgery

or die than those with suspected disease, the lower risk of confirmed disease in the human milk fed group is of potential clinical importance.

This study also supported the hypothesis that the possible benefits of human milk were greater in babies over 30 weeks gestation. Thus above 30 weeks gestation infants feed exclusively on human milk had less than half the rate of confirmed disease than those who were not exclusively human milk-fed (29%-vs-62% with confirmed disease respectively).

Mortality was also significantly lower in predominantly human milk-fed infants than those fed predominantly formula in the subgroup 30 weeks gestation or above (5% -vs- 26%, $p<0.05$).

In summary the survey provides further evidence in support of a protective role of breast milk against necrotising enterocolitis. Disease severity was reduced in those fed predominately or exclusively on human milk; and we found evidence in support of the hypothesis that human feeding is associated with the most marked benefits at 30 weeks gestation or above, in whom mortality from NEC was substantially reduced in predominately human milk-fed infants. These data add weight to the view, based now on several lines of evidence, that the inclusion of human milk in the diets of preterm infants may be clinically beneficial.

Further data and information will be included in the paper currently be prepared for publication. Additional references are available from the researchers.

Reference

1 Lucas A, Cole TJ. Breast milk and neonatal necrotising enterocolitis. Lancet 1990; **336**: 1519-23

Professor A Lucas, Ms R Abbott. MRC Childhood Nutrition Research Centre, Institute of Child Health, 30 Guilford Street, London WC1N 1EH
Tel: 0171 831 9903.

8 International developments

Historical background

The origins of the first national paediatric surveillance unit, the British Paediatric Surveillance Unit (BPSU), can be traced back to 1979-83. Attempts by the British Paediatric Association and the Public Health Laboratory Service in that period to undertake surveillance of necrotising enterocolitis, Reye's syndrome, Kawasaki disease, haemolytic and haemorrhagic shock syndromes relied on passive reporting. Paediatricians were asked to remember and report cases of rare conditions when they were diagnosed. The relative failure of this surveillance led to the development of an active alternative, sending paediatricians monthly reminders of the conditions they were being asked to report - the basis of the current system. The BPSU began formally in 1986, following a 'birth notice' in 'The Times'. It has been continuously in action for over a decade with aims that have evolved to the following:

- to facilitate 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.
- to lessen the burden on doctors of request for reporting
- to increase awareness of the less common disorders of childhood among paediatricans
- to respond 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 are eight other units covering nine countries (the BPSU covers the UK and Eire) using 'active' surveillance system approach to monitor rare disorders in a total child population (age under sixteen years) of around 47 million (Table 10).

A number of units have come to be studying the same or related conditions (Table 9); *congenital rubella* (five countries), *diabetes* (three countries) *haemolytic uraemic syndrome* (three countries) *HIV/AIDS* (four countries), *invasive haemophilus influenzae infection* (two countries) *vitamin K deficiency* (four countries) and most recently *Creutzfeldt-Jakob disease* (two countries). These approaches have not necessarily been coordinated or exploited to their full potential. More recently the units in Europe (British, Netherlands, Germany and Switzerland) have developed a particularly close liaison. A meeting of the European Units was held in Leiden (Netherlands) during January 1995 with better coordination in view. 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, in order to pool data. This is not easy to achieve and though support for such coordination was sought from the European Union Biomed programme, despite favourable comments from referees, funding was not forthcoming in 1997.

Australian Paediatric Surveillance Unit (APSU)

In Australia, separate State Health systems with differing methods of data collection and geographical isolation of paediatric units has hindered collection of national epidemiological information. The Australian Paediatric Surveillance Unit (APSU) has overcome many of these problems. It was established in 1992 and is a Unit of the Australian College of Paediatrics and commenced national active surveillance in 1993. It has been utilised by over 70 individual researchers and a number of National and State organisations.

In 1996, 93% of over 900 cards were returned each month, response rates being similar for different States and specialty groups. This represents an increase from 88% in 1993. The mailing list includes general paediatricians 38%, paediatric subspecialists 42% and other clinicians, including paediatric surgeons and community child health physicians 20%. In contrast to the British scheme monthly report cards are reply-paid, no identifying patient data is provided by clinicians to researchers (a unique identifying code is used to detect duplicate reports) and researchers are not charged for use of the system. The APSU is primarily funded by the Financial markets Foundation for Children with added support from the National Centre for Disease Control.

Eighteen conditions have been studied to date including communicable and vaccine preventable diseases (HIV/AIDS, congenital rubella, congenital and neonatal varicella, poliomyelitis (acute flaccid paralysis), haemolytic uraemic syndrome, neonatal herpes simplex virus infection, subacute sclerosing panencephalitis). Others monitored because of their public health importance include drowning or near drowning and haemorrhagic disease of the newborn. The need for provision of services has been highlighted by the studies on childhood dementia, Rett syndrome and extrahepatic biliary atresia studies. Other conditions under study include Kawasaki disease, arthrogryposis multiplex congenita, congenital adrenal hyperplasia (CAH), Hirschsprung's disease and severe combined immunodeficiency (SCID). In 1997 SCID will be monitored as one of a number of primary immunodeficiency disorders (PID).

The study of *haemolytic uraemic syndrome* (HUS) study has provided important information on the national distribution and aetiology of this disease with simultaneous documentation of epidemic and sporadic cases. In contrast to Europe and North

America E.coli 0157 is not the predominant pathogen - the epidemic cases were mostly attributed to E.coli 0111 and non-epidemic cases to a variety of other shigelle-toxin producing organisms.

The *congenital and neonatal varicella* study identified 28 cases of neonatal varicella and four of varicella embryopathy within 20 months. Prior to this study only three reports of varicella embryopathy were documented in the Australian literature. It is intended that this study will inform decisions regarding the need for varicella immunisation in Australia for non-immune women prior to pregnancy.

Issues of diagnostic classification have been highlighted by the *childhood dementia* study. The majority of children identified had dementia of unknown aetiology. The case definition has been modified for us in the British study on progressive intellectual and neurological deterioration in children (PIND). The *Rett syndrome* study identified a possible specific radiological abnormality and has prompted further research into the pharmacological management of this condition. Surveillance of *congenital adrenal hyperplasia* has been included to allow evaluation of a pilot neonatal screening program for this disorder in New South Wales.

Recent identification of genetic defects associated with *Hirschsprung's disease* highlighted the fact that the incidence of this condition in Australia was unknown. It is intended that this study will investigate the family history of affected children and clarify the range of clinical problems they experience. Attempts to establish a register of *primary immunodeficiency disorders* (PID) in childhood have not been successful in Australia, prompting collective reporting of these conditions to the APSU. Clinicians report a case of PID when they see a child with one of the many disorders of immune function included in this study. They are then asked to only provide information to identify the case and to nominate the immunologist caring for the child. This innovation was introduced to decrease the burden of work for notifying general paediatricians particularly with regard to investigation results needed for the study.

Contacts

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Canadian Paediatric Surveillance Programme (CPSP)

Following discussions with the BPSU, the Canadian Paediatric Surveillance Programme, (CPSP) was set up in 1996. 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 a First Nation (aboriginal) and provincial public health bodies. These represent the strong provincial subdivisions within Canada and publications and circulars have to be in both English and French.

Approximately 1800 paediatricians are circulated monthly with an average response rate of 76%, though there is substantial regional variation. This is consistant with the compliance with newly established units and it is expected rise over the coming year. Though following the methodology of the BPSU there is a difference in style, the CPSP has a more 'hands on' approach with CPSP staff preparing questionnaires with the collaborators (rather than the other way round with the BPSU). The CPSP also issues, collects and analyses the questionnaires. The charges to researchers reflect this increased input. It is appreciated that once the system is more established such close support may no longer be possible. Studies currently being undertaken include surveillance for streptococcal B infection, acute flaccid paralysis, congenital rubella, Creutzfeldt-Jakob disease, haemorrhagic disease of the newborn, neural tube defects, and SSPE. The CPSP have recently produced their first Annual report and copies are available on request.

Contacts

Dr Victor Marchessault, Canadian Paediatric Surveillance Programme, Canadian Paediatric Society, 100-2204 Walkley Road, Ottawa ON KIG G48, Canada
Tel: ++613 526 9397 Fax: ++613 526 3332 Email: cpsp@cps.ca
Dr Paul Socket, Bureau of Infectious Diseases, Laboratory Centre for Disease Control, Ottawa, Ontario, K1A 0L2
Tel: ++613 941 1288 Fax: ++613 998 6413

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 with what has one of the largest child population of any of the units (around 11 million). The surveillance systems differs from the original British methodology in that cards are sent to department heads to complete. The response rates have risen significantly for the 500 clinicians circulated from 75% in 1992 to 92% in 1996 and the follow-up rate to questionnaires is currently 60-90% (Table 10).

Twelve studies have been undertaken these include invasive infection with haemophilus influenzae type b, Reye's syndrome, neonatal thrombosis, Ondine's curse (primary failure of respiratory regulation), Kawasaki disease, acute renal failure, acute liver failure, 50 cases per year are being observed; auto-immune hepatitis, with some 20-30 new cases are reported a year; insulin dependent diabetes mellitus in under five's, incidence rates are now similar to the UK and Ireland 99.1/100,000); pertussis complications, here numbers are falling, this may be due to better vaccination (almost all children are now given the acellular vaccine). Currently there are nine conditions under surveillance are as shown in Table 10.

Contacts

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Prof E Schmidt, Universitats-Kinderklink, Moorenstrasse 5, 4000 Duseldorf 1, Germany

Latvian Paediatric Surveillance Unit

This unit was set up in 1996 by the Latvian Paediatric Association following communications with the BPSU. With a population of just 2.4 million and a birth rate of 20,000 children, individual cases of rare disorders are very low eg. one of aplastic anaemia, 3-5 coeliac disease, 15-20 cases of leukaemia and 30 cases of primary diabetes in one year. In 1996 one case of nesidioblastosis and one case of adrenoleukodystrophy were seen.

Contact

Dr E Bikis, Children's Hospital, 45 Viembasgatve, LY-1004, Rige, Latvia

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 is the only unit in a developing country and 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 6% of respondents have never returned a card. Initially three conditions are under surveillance, paediatric HIV and AIDS, neonatal meningitis and death from asthma.

Contact

Dr Jacqueline Ho, MPA Secretariat, Institut Pedatrik, Hospita Kuala Lumpur, 5074 Kula Lumpuar, Malaysia

Netherlands Paediatric Surveillance Unit (NSCK)

The Dutch Unit started surveillance in October 1992 and is an activity of the Dutch Paediatric Association. Around 360 paediatricians in 152 general hospitals receive the monthly card. The child population is 2.8 million (Table 11). 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 92% in 1996. The follow-up rate is also high at 93%. The importance of full case ascertainment has been realised. Where possible alternative complementary data sources have been recruited for particular disorders for example surveillance of diabetes was strengthened by inclusion of the Dutch Diabetic Association. Surveillance of invasive haemophilus influenzae infection was improved by use of reports from the Netherlands Reference laboratory for bacterial meningitis.

Sixteen studies are either underway (ten) or have been completed (six): these include acute flaccid paralysis, coeliac disease, insulin dependent diabetes mellitus, invasive haemophilus influenzae infection, haemolytic disease of the newborn (non ABO nonrhesus), haemorrhagic disease of the newborn, HIV/AIDS, neural tube defects, postneonatal mortality in premature and smaller-for-dates infants, sickle cell disease and thalassemia major, pertusis, group B streptococcal infection, and venous thrombo-embolic complications. The ten current conditions under surveillance are as shown in Table 10.

Every two years a report is produced; the latest is for the years 1994 and 1995. In 1994, 21 clinicins reported one case, 31% reported 2-4 cases, 11% reported five or more cases, while 37 did not encounter a case of the condition under surveillance.

Contact

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Swiss Paediatric Surveillance Unit (SPSU)

The SPSU was established in early 1995 under the auspices of the Swiss Paediatric Association (SPA) and the Federal Office of Public Health. Report cards are circulated to hospital or clinic based paediatricians (i.e. not to those delivering primary care) and there are approximately 500 respondents in all 39 training/teaching hospitals and clinics, covering a total child population of 1.3 million children. Current compliance rates for return of the orange card is 98%. The six current conditions under surveillance are acute flaccid paralysis, congenital rubella syndrome, congenital toxoplasmosis, haemolytic uraemic syndrome, periventricular leucomalacia and vitamin k deficiency bleeding (Table 10).

Contact

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Developing Units

Several other countries are either considering or developing equivalent surveillance systems these include Papa New Guinea, Portugal, the Czech Republic, Hungary, New Zealand, Japan and Turkey. One surprising omission is the United States where despite federal support being offered for sentinel clinician based reporting recently becoming available through the Centers for Disease Control and Prevention no paediatrician-based surveillance seems to be under development.

***Table 10** National Paediatric Surveillance Units - Conditions under surveillance 1997*

Australia APSU	acute flaccid paralysis arthogryposis multiplex congenita congenital adrenal hyperplasia congenital and neonatal varicella congenital rubella haemorrhagic disease of the newborn (vitamin K deficiency) Hirschsprung's disease HIV/AIDS Kawasaki disease neonatal herpes simplex primary immunodeficiency disorders SSPE
Canada CPSP	acute flaccid paralysis congenital rubella Creutzfeldt-Jacob disease haemorrhagic disease of the newborn neural tube defects SSPE
Germany ESPED	automimmune hepatitis fatal and near fatal asthma haemorrhagic shock encephalopathy syndrome idiopathic thrombocytopenia insulin dependent diabetes (age <5y) mulitple sclerosis systemic pneumococcal infection varicella complications vitamin K deficiency bleeding
Malaysia MPSU	death from asthma HIV/AIDS neonatal meningitis
Netherlands NSCK	accute flaccid paralysis coeliac disease diabetes mellitus HIV/AIDS Invasive haemophilus inflenzae neural tube defects post neonatal mortality in premature and dysmature babies pertussis group B streptococcal infections venous thromboembolic complications
Swiss SPSU	accute flaccid paralysis congenital rubella congenital toxoplasmosis haemolytic uraemic syndrome periventricular leucomalacia vitamin K deficiency bleeding
UK & Eire BPSU	cerebral oedema following diabetic ketoacidosis congenital rubella haemolytic uraemic syndrome hepatitis C infection HIV/AIDS invasive *haemophilus influenzae* neonatal meningitis progressive intellectual and neurological deterioration pyridoxine dependent seizures Reye's syndrome SSPE

***Table 11** National Paediatric Surveillance Units Status circa end 1996*

	Commencement	Child Population (million - aged 0-15yrs)	Respondents	Average response rate 1996
Australian	1993	3.9	960-1000	>93%
Canadian	1996	6.0	2100	76%
German	1992	11.0	500	92%
Malaysian	1992	7.6	340	94%
Netherlands	1994	2.8	300	92%
Swiss	1995	1.3	40 clinics	98%
UK & Eire	1986	12.8	1600	94%

9 BPSU scientific seminar

The second scientific meeting of the BPSU, held on 4 December at the Royal College of Physicians (London) was a considerable success. Attenders were welcomed by Professor David Baum (President elect) to what he pointed out was the first meeting of the new Royal College of Paediatrics and Child Health. Over one hundred paediatricians, researchers and epidemiologists attended. There was representation from sister paediatric surveillance units in Malaysia, Australia and Canada, through the form of posters as well as displays from or relating to the Scottish Centre for Infection and Environmental Health, the Welsh Paediatric Surveillance System, Contact a Family, childhood AIDS/HIV, meningococcal disease, European paediatric surveillance units and Rett syndrome.

The morning session opened with a presentation from Professor Catherine Peckham describing the mechanism and impact of the BPSU. Taking surveillance of childhood HIV and AIDS as an example, emphasis was placed on the importance of multiple case ascertainment. This is an area which the Unit wishes to strengthen as experience shows that multiple ascertainment, if data linkages are possible, improves data quantity and quality. The body of the meeting focused on selected BPSU projects and their impact on child health.

Professor James Leonard of the Metabolic Unit, ICH (London) describing the results of the 1994-96 Medium Chain acyl-CoA dehydrogenase deficiency (MCAD) survey, opened this part of the meeting. He explained that MCAD is the most frequent inherited disorder of fatty acid oxidation that presents with an episode of acute metabolic encephalopathy and hypoketotic hypoglycaemia. During the period of surveillance 56 patients were identified. Six patients died. There were also a further four deaths in siblings where MCAD was strongly suspected as the underlying cause. A regional comparison of dried blood spots suggested that some cases were going undiagnosed or were entirely asymptomatic.

Dr Ed Wraith, (Director, Willink Biochemical Genetics Unit) followed with a review on evaluating children with metabolic disease. The four most common modes of evaluation and their investigation required were described and a convincing case was made for long term management that requires specialist medical, dietary and biochemical services best being undertaken or directed by regional centres with the appropriate expertise.

The second pair of presentations examined congenital rubella and the impact of the MR campaign of 1994. Ms Pat Tookey (ICH, London) summarised the results of the congenital rubella surveillance programme, in existence since 1971, and through the BPSU since 1986. A fall in the number of reports from 200-300 per year in pre-vaccination days to around 40 by 1990 was noted.

Dr Elizabeth Miller (PHLS) then described how the 1994 measles/rubella immunisation programme was initiated and implemented. The origins of which were low measles vaccine coverage of the 70's and 80's and the fact that immunisation is only 90% effective in conferring individual protection. Particular credit was given to the School Health Service which provided the manpower and the Department of Health who coordinated the implementation. Over seven million school aged children were vaccinated within a month. It followed mathematical models predicting an epidemic in early 1995-96 to occur predominately in older children. In the talk Dr Miller showed how seroepidemiology had predicted the epidemics and then how the campaign resulted in a near total interruption of measles transmission in the UK; most cases now occurring originate abroad. A question that arose in discussion was whether, given the reduction in numbers of nurses and doctors, the School Health Service would have sufficient manpower in the future to repeat any emergency provision like that of the MR campaign.

The afternoon session began with Dr Andrew McNinch presenting results of the Vitamin K Deficiency Bleeding (VKDB) surveys of 1987 and 1993. The second study identified 31 cases of VKDB; 18 occurred after one oral dose, two after three oral doses and one after 100micrograms intramuscularly. Ten babies had received no prophylaxis (consent withheld in 4). He also covered topics of action of vitamin K, apart from those on coagulation, the unphysiological blood levels of vitamin K produced by current prophylaxis regimens, the importance of early detection of liver disease and the prompt investigation needed of apparently trivial "warning bleeds". Finally, the need to continue encouraging breast-feeding was emphasised.

Professor Roy Meadow summarised the Munchausen syndrome by proxy/non-accidental suffocation and poisoning survey (MSPB/NAPS). One hundred and twenty-eight cases were identified, during the surveillance period, giving an annual incidence rate of at least 2.8 per 100,000 children aged under one. Approximately half the cases of smothering, and two thirds of the cases of poisoning occurred in the context of MSBP. There was an 85% probability of 'certain' diagnoses by paediatricians. Regional variations suggest that there is an under estimate of the true incidence rate, an area which needs to be examined by the BPSU and investigators.

Finally, Professor Neil McIntosh, the chairman of the RCPCH Ethics Advisory Committee, gave an overview of the ethical issues arising from surveillance and research. He used the occasion to note the continuing lack of a national ethics committee and to propose that the College organise regional multidisciplinary committees that would review proposals for groups of district level committees, a proposal that subsequently has been acted upon by the NHS.

Copies of the abstracts are available from the BPSU office and the Unit would like to thank Pasteur Merieux MSD and Serono for their financial support of the meeting.

Appendix A Completed studies prior to 1996

By mid 1996 the British Paediatric Surveillance Unit had completed twenty-nine 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. **Transient and permanent neontal diabetes**
    (July 1994 - August 1995)
    Dr J Shield, Professor J D Baum
29. **Adverse neonatal outcomes of delivery or labour in water**
    (April 1994 - April 1996)
    Ms P Tookey, Dr R Gilbert

Appendix B Recent publications

Published papers

Hardie JRM, Newton LH, Bruce JC, Glasgow JFT, Mowat AP, Stephenson JBP, Hall SM. The changing clinical pattern of Reye's syndrome 1982-90. Arch. Dis. Child. 1996; **74**: 400-405

McClure RJ, Davis, PM, Meadow SR, Sibert JR. The epidemiology of Munchaussen Syndrome by Proxy, Non-accidental poisoning, and Non-accidental suffocation. Arch. Dis. Child. 1996; **75**: 57-61

Dezateux C, Godward S. A national survey of screening for congenital dislocation of the hip. Arch. Dis. Child. 1996; **74**: 445-448

Dezateux C, Godward S. Validation of the reporting bases of the orthopaedic and paediatric surveillance schemes. Arch Dis. Child 1996; **75**: 232-236

MacDonagh SE, Masters JM, Helps BA, Tookey PA, Ades AE, Gibb DM. Antenatal HIV testing in London: policy, uptake and detection. BMJ 1996; **12**: 532-3

Temple IK, Gardiner R, Kibirige MS et al. Further evidence for an imprinted gene for neonatal diabetes located to chromosome 6q 22-2. Hum. Mol. Genet. 1996; **5**: 1117-121

Salisbury DM, Ramsay ME, White JM, Brown DW. Polio Eradication:Surveillance Implications for the United Kingdom. The Journ. of Infect. Disease 1997; **175** (Suppl 1): S156-9

Booy R, Heath PT, Slack MPE, Begg N, Moxon ER. Vaccine failures after primary immunisation with Haemophilus influenza type-b conjugate vaccine without booster. Lancet 1997; **349**: 1197-202

Miller E, Waight P, Gay N, Ramsay M, Vurdien J, Morgan-Capner P, Hesketh L, Brown D, Tookey P, Peckham C. The epidemiology of rubella in England and Wales before and after the 1994 measles and rubella vaccination campaign: fourth joint report from the PHLS and the National Congenital Rubella Surveillance Programme. CDR Review 1997; **7**: No.2 R26-R32

Tookey P, Peckham C. Neonatal herpes simplex virus infection in the British Isles. Paediatric and Perinatal Epidemiology 1997; **10**: 432-442

Shield JPH, Gardner RJ, Wadsworth EJK et al. Aetiopathology and genetic basis of neonatal diabetes. Arch. Dis. Child. 1997; **76**: F39-F42

Mucklow ES, Chemistry Set Poisoning. Internat. Journ. Clin. Pract. 1997; **51.5**: 321-23

Pollitt RJ, Green A, McCabe CJ *et al.* Neonatal screening for inborn errors of metabolism: cost, yield and outcome. *Health Technology Assessment Report*

Appendix C Recent presentations

BPA Annual Scientific Meeting 1996

Surgery for congenital dislocation of the hip in children aged 5 and under in the UK.
Godward S, Dezateux C.

Neonatal diabetes: clinical characteristics, aetiopathogenisis and long term implications.
Shield JPH, Temple IK, Wadsworth EJK, James RS, Howell WM, Baum JD.

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.

Antenatal HIV testing in London: Policy, uptake and prevalence.
MacDonagh SE, Masters J, Helps BA, Tookey PA, Ades AE, Gibb DM.

2nd BPSU Scientific Seminar 1996

Survey on medium chain acyl CoA dehydrogenase deficiency.
Leonard J.

Evaluation of the child with suspected metabolic disease.
Wraith JE.

Survey of congenital rubella.
Tookey PA.

The MR Campaign November 1994 - its design, implementation and results.
Miller E.

Vitamin K deficiency bleeding.
McNinch A.

Issues relating to prophylactic vitamin K.
Hull D.

Munchausen syndrome by proxy & non-accidental poisoning/ suffocation.
Meadow SR.

Research, surveillance and audit; the ethical issues.
McIntosh N.

1st RCPCH Annual Scientific Meeting 1997

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

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

Abstracts and conferences proceedings

European Society for Paediatric Research Annual Meeting 1996

Surveillance of paediatric HIV in the UK: multiple source ascertainment. European Society for Paediatric Infectious disease, Elsinore, Denmark 1996.
Tookey PA, Nicoll A, Ades AE, Goldberg D, Duong T, Mortimer J,Berry T, Peckham CS.

European Surveillance of rare infectious disease. European Society for Paediatric Infectious disease, Elsinore, Denmark 1996.
Lynn RM, Hirasing R, von Kries R, Zimmerman, HP.

Obstetric and Paediatric surveillance in the United Kingdom. International HIV/AIDS conference, Vancouver, Canada 1996.
Ades AE, Tookey P, Duong T, Berry T, Goldberg D, Nicoll A.

Evaluation of the antenatal HIV testing in London, UK (poster). International HIV/AIDS conference, Vancouver, Canada 1996.
Gibb DM, MacDonagh SE, Masters J, Helps BA, Gupta R, Tuck P, Tookey PA, Peckham C, Ades AE.

National surveillance of adverse neonatal outcomes following labour or delivery in water. Waterbirth conference, Southampton 1996.
Gilbert R, Tookey PA.

Ultrasound imaging of the neonatal hip: increase use of unevaluated technology. International Society of Technology. Assessment in healthcare. San Francisco. June 1996.

French Academy of Paediatrics Meeting 1996

Kawasaki Disease in the UK.
Rudd P.

Appendix D Support groups for rare childhood disorders

Congenital Dislocation of the Hip
STEPS, 15 Statham Close, Lymm, Cheshire, WA12 9NN.

Congenital Rubella
National Rubella Council, 33-39 Pancras Road, London NW1 2QB.

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

Dermatomyositis & Polymyositis
Dermatomyositis & Polymyositis Support Group, 146 Newtown Road, Woolston, Southampton, Hampshire, S02 9HR.

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

Galactosaemia
Galactosaemia Support Group, Mrs S Bevington 31 Cotysmore Road, Sutton Coldfield, W Midlands B75 6BS.

Guillain-Barre Syndrome
Guillain-Barre Syndrome Support Group, CC Offices, Eastgate, Sleaford, Lincolnshire, NG34 7EB.

Histiocytosis
Histiocytosis Support Group UK, 23 Maple Grove, Woburn Sands, Milton Keynes MK7 8QN.

Kawasaki Disease
Mrs S Davidson, 13 Norwood Grove, Potters Green, Coventry, CV2 22FR.

Liver Disease
Children's Liver Disease Foundation, 40-42 Stoke Road, Guildford, Surrey GU1 4HS.

Lowe Syndrome
Lowe Syndrome Association, 29 Gleneagles Drive, Penworthan, Preston, Lancashire, PR1 0JT.

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

Neonatal Herpes
Herpes Association, 41 North Road, London N7 9DP.

Poliomyelitis
Mr L Jackson, British Polio Fellowship, Unit A, Eagle Office Centre, The Runway, South Ruislip HA4 6SE.

Rett Syndrome
The Rett Syndrome Support Group, Mrs Y Milne, Heartpool, Golden Valley, Castlemorton, Malvern, Worcestershire WR13 6AA.

Reye's 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 OHA.

Appendix E Contact addresses

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British Orthopaedic Association, Lincoln's Inn Field, London SE1 9RT

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Children Nationwide, Medical Research Fund, Nicholas House, London SE1 0LN

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

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