BPSU

Eighth Annual Report 1993

British Paediatric Surveillance Unit

Supported by the Medical Research Fund of Children Nationwide

BRITISH PAEDIATRIC SURVEILLANCE UNIT

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The BPSU positively encourages copying and circulation of this report to colleagues, junior staff, and to medical students.

Additional copies are available from the BPSU office, to which any enquiries should be addressed.

BRITISH PAEDIATRIC SURVEILLANCE UNIT

Eighth ANNUAL REPORT 1993

1 Acknowledgements

As in previous years the Medical Research Fund of Children Nationwide is to be thanked for the continued financial support of the BPSU. We should like to thank the Muirhead Trust for supporting the development costs of new computer equipment and Allen & Hanburys for supplying the protocol booklets.

Thanks are due to the British Paediatric Association for its continued support; finally, we should also like to thank members of the British Paediatric Association, the Faculty of Paediatrics of the Royal College of Physicians of Ireland and the many other clinicians and pathologists 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.

BPSU Executive Committee

December 1994

2 Chairman's review

The British Paediatric Surveillance Unit (BPSU) has been in existence for almost a decade, and is remarkable in its high reporting rate: over 90% of paediatricians return a report card in any one month (Section 4). The importance and effectiveness of the BPSU can be best measured in terms of studies completed, scientific questions answered, reports published, and contributions to public health policy. The value of BPSU studies in raising awareness of uncommon conditions and their management is less easy to measure.

The study of HIV and AIDS in childhood (section 7.1) shows how a BPSU study can answer a range of important questions, and how data gathered directly from the BPSU system becomes more powerful when combined with data from other sources. In this case BPSU data, information from a national obstetric register of pregnancies complicated by HIV, and unlinked monitoring of HIV infection showed that only 10% of HIV-1 infections in pregnant mothers in London in 1993 had been clinically detected by the time they gave birth. This information has contributed to deliberations about antenatal screening for HIV infection. The study has also shown that *pneumocystis carinii* pneumonia in early infancy is the most commonly reported manifestation of AIDS in children and is associated with a poor prognosis. This study has served as a basis for the recruitment of patients into therapeutic trials of new antiviral drugs.

Reye's syndrome has been monitored by the BPSU since 1986 (Section 7.2) and the study has shown that the incidence declined after it was recommended that aspirin should not be given to children under the age of 12. Another important finding was that a large proportion of the small number of cases still reported through the BPSU are caused by one of a number of inherited metabolic disorders. This emphasises the need for paediatricians to consider such diagnoses and illustrates the educational role of the BPSU.

The fact that so few cases of congenital rubella (three in 1993) were reported to the BPSU reflects the effectiveness of the immunisation programme (Section 7.4). It is particularly important that monitoring should continue, to determine whether the marked increase in rubella infections in 1993 is followed by an increase in the number of affected babies, and to monitor the effect of changing immunisation strategies (from the targeting of schoolgirls to mumps, measles, and rubella vaccines in early childhood and the current measles and rubella vaccination campaign in schoolchildren).

Two other studies have investigated the direct effects of immunisation programmes. The study on acute flaccid paralysis (Section 7.7) aimed to identify reported cases of acute flaccid paralysis in children due to vaccine-associated polio virus infection: only three such cases occurred in the United Kingdom and the Republic of Ireland in 1993. In addition, one case was not associated with vaccine, the infection having been acquired abroad. Active case reporting is required for certification by the World Health Organisation and this study has contributed to declaring the United Kingdom and the Republic of Ireland free of indigenous polio.

The introduction of vaccine against *Haemophilus influenzae* type b (Hib) is another recent success for child health. Laboratory reports of invasive Hib infections have declined since vaccination began in 1992. Natural changes in the incidence of infectious diseases can occur and without the BPSU study direct estimates of the effectiveness of the conjugate vaccine would not be available. This year's results (section 7.12) have shown a high level of vaccine effectiveness, but that children with specific clinical conditions have a greater risk of vaccine failure. This survey, like those for HIV and congenital rubella, emphasises the importance to BPSU investigators of using multiple reporting systems. In this case laboratory reporting by microbiologists was essential; reliance on the BPSU or laboratories alone would have resulted in many cases being missed. The United Kingdom is unusual in that a booster dose of Hib vaccine is not scheduled. The extension of the Hib survey of the BPSU into 1994 and beyond will monitor the effectiveness of this policy.

The study of the epidemiology of juvenile dermatomyositis (Section 7.6) found that the annual incidence of this rare condition was about two per million children and that it was four times more common in girls than boys. A follow up study is underway to see whether the initial clinical presentation or treatment affected prognosis.

Androgen insensitivity syndrome (Section 7.8) is a rare condition, in which a genetically male child is born with female features. The BPSU study was completed in 1993: 49 cases were identified in two years. Many children with partial androgen insensitivity syndrome were being raised as males despite a recommendation that they should be raised as females. As in many BPSU surveys, the researchers are planning long term follow up to observe the outcome for these children.

The study on vitamin K deficiency bleeding (Section 7.13) was re-launched urgently in 1993 in response to a rapid trend towards the use of oral vitamin K in newborn babies. This came about as a result of concerns about a possible association between intramuscular vitamin K and subsequent childhood cancers, not confirmed by later studies. Analysis of the results is not yet complete but, compared with the previous BPSU study in 1989-90, a larger proportion of babies with vitamin K deficiency bleeding had been given oral vitamin K and a smaller proportion had received none at all.

The study of congenital dislocation of the hip (CDH) was the largest and most intense study the BPSU has yet conducted. The aim was to determine how well the current screening programme works, what happens to babies whose tests suggest they have the condition, and how many cases are missed by the test. Although the study was brief (four months), the condition has a high incidence and the volume of reports caused a considerable strain on the BPSU office. The number of questionnaires completed by members of the BPA and other reporters (orthopaedic surgeons) constituted a heavy workload for all concerned. We are very grateful for the way they responded to the challenge and made over 900 reports in the four months of the study. Results are awaited but the study raised questions immediately about the role of ultrasound in the screening and management of CDH.

It is known that early operative treatment for biliary atresia (section 7.15) improves the long term outcome. The principal aims of the biliary atresia study are to find out how common this condition is, and the age at which babies are diagnosed and treated. These important data will contribute to the debate about whether 'yellow alert' screening for jaundice in infants is justified.

The BPSU's success and value is recognised nationally and internationally if imitation is anything to go by. Similar surveillance units have been established among British neurologists and occupational health physicians. Overseas, surveillance units based on the BPSU are now well established in Australia, the Netherlands, and Germany.

Several changes have taken place within the BPSU in 1993 and 1994. The number of consultant paediatricians has risen: the BPSU administration has had to keep pace with a 6% rise in the number of respondents on the mailing list, which numbered 1218 at the end of 1993. There have been administrative changes too. Firstly, the BPSU has become a part of the new British Paediatric Association Research Unit. Secondly, Sue Hall has left and it is a measure of her contribution as medical advisor that she has been replaced by two people, Ruth Gilbert from the Institute of Child Health, London and Angus Nicoll of the Public Health Laboratory Service. I am grateful to them both, and to their institutions for releasing them in order to assist the BPSU. Richard Lynn the scientific coordinator, and Myra Schehtman his assistant, are the core of the unit and it is rarely appreciated how many hours they put into its work. I should also like to thank the members of the Executive Committee and the Joint Committee of Management. The Executive Committee deserves particular mention as its members give up many Fridays in the year for their committee work.

Professor Catherine Peckham
Chairman BPSU Executive Committee

3 Introduction

The British Paediatric Surveillance Unit (BPSU) began its work in June 1986, and covers paediatricians in the United Kingdom and the Republic of Ireland. The BPSU enables paediatricians to participate in the surveillance of infections and infection-related conditions and promotes the study of uncommon disorders. It provides a mechanism by which new diseases can be detected, monitored and investigated swiftly.

Several agencies collaborate in the BPSU: the British Paediatric Association (BPA), the Public Health Laboratory Service (PHLS), the PHLS Communicable Disease Surveillance Centre (CDSC), and the Department of Epidemiology at the Institute of Child Health, University of London (ICH), the Scottish Centre for Infection and Environmental Health in Glasgow (SCIEH), which administers the scheme in Scotland, and the Faculty of Paediatrics of the Royal College of Physicians (Ireland). The BPSU monitors conditions of importance to public health, and observers from the Department of Health and the Office of Population Censuses and Surveys (OPCS) attend BPSU committee meetings.

The reporting system

Participants of the reporting system include consultant paediatricians who are members of the BPA, the Faculty of Paediatrics of the Royal College of Physicians of Ireland, and since 1992, selected members of other specialties. The BPSU has extended its activities through a study on congenital dislocation of the hip undertaken with the British Orthopaedic Association (BOA) and instigated by the Medical Research Council in 1993.

Participants are sent a card each month, on which is listed the disorders under surveillance, and a set of instructions. They are asked to return the card to the BPSU office each month, reporting the number of cases of each disorder they have seen in the preceding month. Compliance with the scheme is constantly monitored. Case reports are then followed up. The BPSU office informs the relevant research team who contact the reporting paediatrician for further information in accordance with a study protocol for the condition reported. The research team then report back to the BPSU on the outcome of the follow up, confirming cases, identifying duplicates and reporting errors. The research teams are employed not by the BPSU but by the institution undertaking the research.

A distinctive and powerful feature of the BPSU system is the use of complementary sources of information alongside data from paediatricians. This allows validation of both sources and gives a more complete picture of a disease or condition. The first complementary source to be used were laboratory reports of infections from the PHLS; this has been extended to other sources such as death entries (OPCS) and hospital episodes system data. When multiple sources of data are considered it seems that ascertainment of total numbers of cases is high, though completeness varies considerably between studies and conditions according to the ease of ascertainment and the availability of complementary sources.

This report covers the calendar year 1993, but also refers to studies that began in 1994.

4 How the BPSU works

4.1 Selection of studies

A study is eligible for participation in the scheme if its subject is a rare childhood disorder (or rare complication of a more common disease) of such low incidence or prevalence as to require ascertainment of cases on a national scale in order to generate sufficient numbers for the study. Particular priority is given to studies of public health importance though 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 limited and competition for a place on the BPSU card in the past year was keen. In 1993 the capacity of the reporting card was increased to accommodate 14 rather than 12 conditions. The unit receives an average of 30 general enquiries a year; many are eventually incorporated into the reporting card. There are currently about 25 studies in various stages of development.

In order to process applications quickly the unit has recently adopted a two phase procedure. In phase one a short study protocol is submitted, no longer than two sides of A4. This should include background to the proposed study, a case definition, questions that the study aims to answer, and details of financial and academic support. The scientific coordinator and medical advisers can offer guidance on submitting an application before it is presented to the BPSU Executive Committee (BEC).

For the following reasons many studies are found to be unsuitable at phase one; the condition may be too common thus placing too great a burden on paediatricians for reporting or follow up; no suitable case definition may be available; the aim of the study may constitute audit rather than surveillance and research; data may be easily obtainable elsewhere. In addition a number of studies clearly present insuperable practical difficulties. Once the BEC agrees that the protocol is suitable, the second phase of the application is requested. This should provide full details of the methodology and aims of the study. The applicant presents the details to the BEC, which meets monthly and mostly consists of consultant paediatricians (general and specialist) and epidemiologists.

Factors that determine whether an application is accepted include:

a) rarity, though short term or geographically limited studies of comparatively more common disorders are considered.
b) proposals with outcomes of clear public health importance.
c) scientific importance.
d) uniqueness, priority will not be given if similar studies have recently been undertaken or if other data sources are much more readily available (though use of alternative data sources for validation is encouraged).
e) quality, in terms of clear achievable objectives, practicability, patient confidentiality, resources.
f) workload placed on the reporting paediatrician.
g) ethical approval where appropriate.

If necessary the BPSU is willing to assist potential investigators (especially those with less experience in research methods) in improving potentially valuable studies.

If a study is not accepted, the BEC will always try to advise the applicant on alternate means of collecting data.

4.2 Mailing system

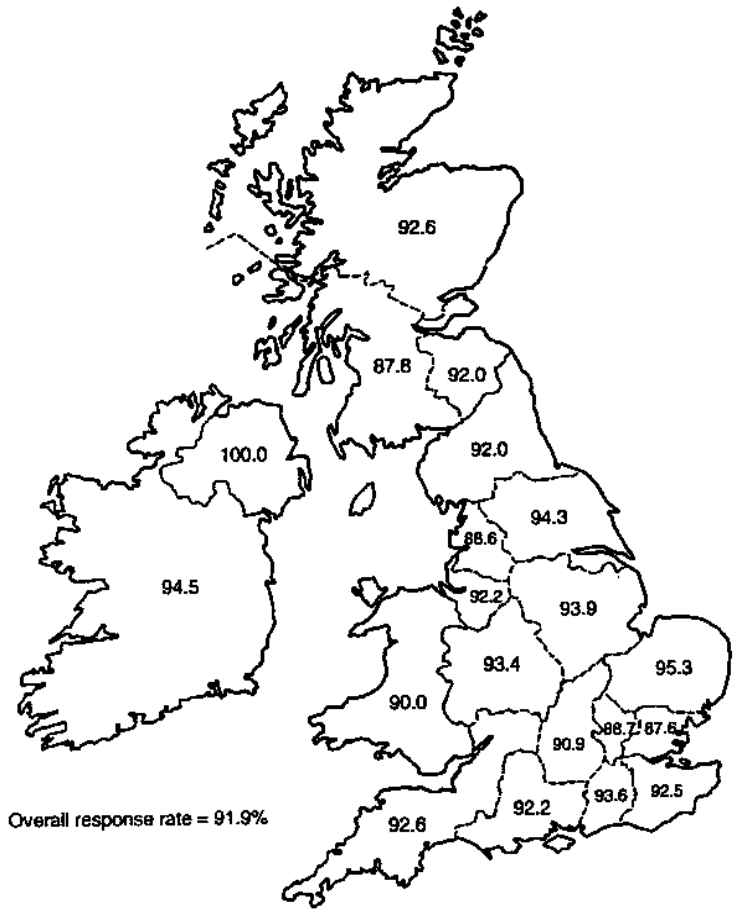
The BPSU works on the principle of 'active' reporting. The stimulus for a clinician to report is a card with a 'menu' of reportable disorders, sent each month by the BPSU office to consultant paediatricians. The office updates its mailing list with changes sent in by members, and through the monitoring of new consultant appointments. The card is accompanied by instructions for reporting and case definitions. When a new study begins, the mailing includes a study protocol with detailed information about the study. The respondents tick boxes against any of the conditions seen in the preceding calender month. If no patients with any of the disorders have been seen, a 'nothing to report' box is marked: this is an essential feature of the system because it monitors compliance and detects non-responders who may have moved or retired. Respondents who have not returned their card for three consecutive months are sent reminders. Scottish paediatricians return their completed cards to the BPSU office by way of the Scottish Centre for Infection and Environmental Health.

4.3 Participation

The number of paediatricians who participated in the scheme in 1993 rose from 1145 to 1218, an increase of about 6% over the year. The response rate, calculated as the percentage of cards returned within sixty days of mailing, was 91.8% (13013/14168) for the year. The range of response rates extended from 82.5% (1021/1162) in April to 94.3% (1085/1151) in February, with a median of 91.9% (2166/2357) in May and June.

Figure 1 shows the mean response rate for each region in 1993. Response rates varied considerably between regions; the region with the highest response rate was Northern Ireland (100%), and North East Thames had the lowest response rate (87.3%). No locality showed a response rate less than 87%. The BPSU has developed additional respondent databases to help ascertain cases of particular conditions that are seen by other specialists as well as paediatricians.

Figure 1 - Average response rate (%) by area, 1993



To help ascertain juvenile dermatomyositis the BPSU set up an additional database in May 1992 to include specialist dermatologists and rheumatologists who are not members of the BPA. In 1993 the mean response rate for dermatologists was 62% and for rheumatologists 63% (Table 1). A group of pathologists joined the BPSU in January 1993. This group is helping to ascertain cases of haemophagocytic lymphohistiocytosis and biliary atresia, a mean response rate of 63% was achieved. Although response rates for these new groups were lower than for BPA members, they still represent a good response for a clinical surveillance system.

Table 1 - Response rate from the non-BPA members of dermatology, rheumatology, and pathology specialty groups

Specialty	Cards Sent	Cards Returned	Percentage (%)
Dermatology	29	18	62
Rheumatology	22	14	63
Pathology	43	27	63

5 Cases reported to the BPSU (up to October 1994)

5.1 Cumulative reports

For the year ending 1993, a total of 1072 cases have been reported (Table 2, overleaf). Five hundred and ninety-five of the 1072 cases have been confirmed as positive reports by the researchers who feed this information back to the BPSU. The figure of 595 will alter as outstanding data is collected. It should be noted that the confirmed cases (to October 1994) in Table 2 exclude report errors and duplicates.

The number of cases in Table 2 may differ slightly from those in the following research articles for reasons of definition, including ascertainment from sources other than the BPSU.

Table 2 - Cases reported: June 1986 to December 1993 (confirmed by October 1994)

Condition under surveillance	Date when reporting began	REPORTS (confirmed)									
		June 1986 to Dec 1987		Jan 1988 to Dec 1989		Jan 1990 to Dec 1991		1992		1993	
AIDS/HIV	June 1986	60	(37)	77	(53)	378	(296)	117	(84)	111	(68)
Reye	June 1986	80	(38)	69	(38)	52	(20)	19	(11)	21	(5)
SSPE	June 1986	50	(32)	34	(18)	45	(26)	11	(4)	13	(6)
Con. rubella	Jan 1991	-	-	-	-	32	(18)	11	(8)	8	(3)
AFP	July 1991	-	-	-	-	49	(33)	50	(38)	37	(28)
AIS	Sept 1991	-	-	-	-	71	(27)	45	(21)	23	(7)
HLH	Sept 1991	-	-	-	-	16	(10)	25	(10)	32	(5)
Derm	May 1992	-	-	-	-	-	-	63	(25)	60	(23)
Hib	Sept 1992	-	-	-	-	-	-	26	(20)	52	(36)
NAPS/MSBP	Sept 1992	-	-	-	-	-	-	36	(26)	121	(68)
VKDB	Jan 1993	-	-	-	-	-	-	-	-	64	(20)
Biliary atresia	March 1993	-	-	-	-	-	-	-	-	73	(10)
CDH	April 1993	-	-	-	-	-	-	-	-	344*	(230)
Con. syphilis	July 1993	-	-	-	-	-	-	-	-	6	(5)
NEC	Sept 1993	-	-	-	-	-	-	-	-	107	(81)
Total		190	(107)	180	(109)	643	(430)	403	(247)	1072	(595)

* excludes BOA reports (see page 32). Tables exclude previously completed studies (see page 39).

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 & Wales which are not followed up by CDSC

AFP = Acute flaccid paralysis

AIS = Androgen insensitivity syndrome

HLH = Haemophagocytic lymphohistiocytosis

Derm = Juvenile dermatomyositis

Hib = Haemophilus influenzae b vaccination failures

NAPS/MSBP = Non-accidental poisoning, suffocation and Munchausen syndrome by proxy

CDH = Congenital dislocation of the hip

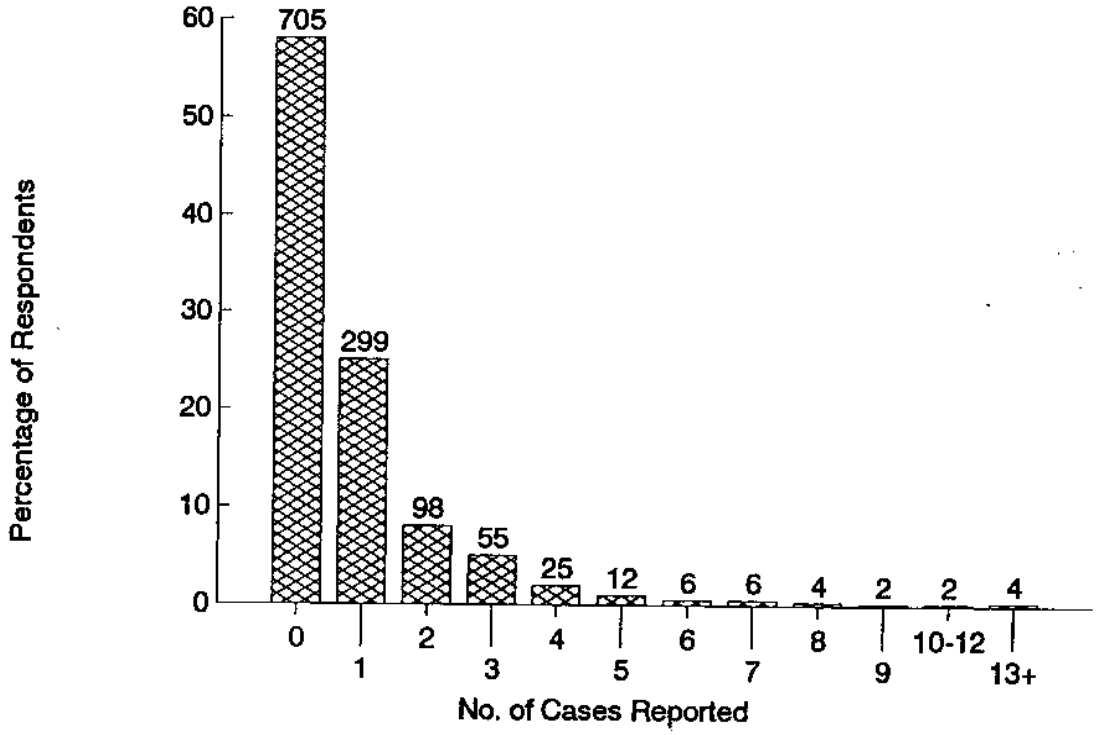
Con. Syphilis = Congenital syphilis

NEC = Neonatal necrotising enterocolitis

5.2 Reports by respondents

The workload of BPSU respondents in terms of reporting and completing follow up questionnaires is continually monitored (Figure 2). Over half of the respondents (58%) did not report a case in 1993; 39% reported between one and four cases, and only 3% reported five or more cases. The two high intensity studies of congenital dislocation of the hip and neonatal necrotising enterocolitis (which began in 1993) placed a particular burden on a small number of individuals who were identifying all of the cases for their district or unit.

Figure 2 - Respondent workload (number of respondents in brackets)



5.3 Follow up and confirmation of notifications

The BPSU sends reports of notifications from clinicians to the appropriate research team, who contact the reporting clinician and elicit further clinical details using a short questionnaire. The researchers then assess the details, informing the BPSU whether or not the case had met the study definition or whether the case had been reported already (this is particularly likely for diseases that require referral). The time taken to follow up a report varies greatly between conditions and may be longer if microbiological/pathological details are needed to confirm a case.

The rate at which notifications are followed up, is encouraging. Of the studies active up to the end of 1993, only 316 of 2488 initial reports (13%) had yet to be followed up and experience has shown that this figure falls as a study nears completion. The final proportion of notifications that are successfully followed up average between 95% and 100%. This very high compliance rate is vital for the success of the BPSU and the individual studies it coordinates.

Table 3 provides evidence for the accuracy of reporting. Four hundred and sixteen (17%) case reports received for the active studies were later identified as reporting errors (misdiagnosis, case definition not met, or wrong box marked on the reporting card).

Table 3 - Outcome of the follow up for cases reported up to December 1993

	REPORTS (%)							
Conditions under surveillance	VALID (%)		INVALID			Not yet known	(%)	TOTAL
			Duplicates	Errors	D+E%			
AIDS/HIV	538	(72)	103	87	(26)	15	(2)	743
Reye	112	(46)	35	90	(52)	4	(2)	241
SSPE	86	(56)	20	26	(30)	21	(14)	153
Cong. Rubella	29	(57)	8	9	(33)	5	(10)	51
AFP*	99	(73)	23	4	(20)	10	(7)	136
AIS	55	(40)	3	44	(34)	37	(27)	139
HLH*	25	(34)	14	1	(21)	33	(45)	73
J Derm	48	(39)	25	34	(48)	16	(13)	123
Hib*	56	(72)	6	16	(28)	0	(0)	78
NAPS/MSBP	94	(60)	13	23	(23)	27	(17)	157
VKDB	20	(31)	4	16	(31)	24	(38)	64
B Atresia	10	(14)	3	5	(11)	55	(75)	73
CS	5	(83)	0	1	(17)	0	(0)	6
NEC	81	(76)	14	12	(24)	0	(0)	107
CDH	230	(67)	0	48	(14)	66	(19)	344
ALL	1488	(60)	271	416	(28)	313	(13)	2488

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

OUTCOME

Valid Report: Case followed up and confirmed by research worker as both unique (that is, not a duplicate) and satisfying the diagnostic criteria. This includes cases reported to the BPSU but already known to the research worker from another source.

Invalid Report: Duplicate report from within the BPSU scheme. Reporting error (for example ticked wrong box, revised diagnosis, uncertain case not meeting definition, or unable to follow up).

Not yet known: Details not yet received by BPSU from research workers (as of October 1994).

6 Funding

The BPSU requests that research teams contribute a monthly sum to the unit. In 1992/93 this was £150 each month, to cover the start up costs of a study, printing, and distribution of cards, and administration for a study. After assessment of the BPSU's future needs the suggested contribution rate has been set at £165 each month for 1993/4. It is felt that the contribution rate should reflect the specific work carried out by the BPSU, and a sliding scale of voluntary charges is currently being considered. For the financial year 1992/3 the total contribution from researchers represented 35% of the total BPSU running costs.

7 Conditions included

This section summarises the background, objectives, and progress of the 15 studies undertaken during 1993. Three studies began in 1994 and these are highlighted elsewhere in this report (Section 8).

Table 4 - Studies undertaken in 1993

Page	Study	Principal researchers	Research institutions
14-15	AIDS/HIV*	Dr C Davison, Dr A Nicoll, Dr D Goldberg	ICH (London), PHLS, SCIEH
15-17	Reye's syndrome*	Dr M Catchpole, Ms L Newton	PHLS
18	Neonatal necrotising enterocolitis	Ms R Abbott, Dr A Lucas	Dunn Nutrition Unit, Cambridge
19-20	Congenital rubella*	Ms G Jones, Ms P Tookey, Professor C Peckham	ICH (London)
20-21	Subacute sclerosing panencephalitis	Dr E Miller, Dr N Begg	PHLS
21-22	Juvenile dermatomyositis	Dr P M Symmons, Dr A J Sills	Royal Liverpool Children's Hospital, ARC Epidemiology Research Unit
23	Acute flaccid paralysis	Dr N Begg	PHLS
24-26	Androgen insensitivity syndrome	Professor I A Hughes	Addenbrooke's Hospital
26-27	Haemophagocytic lymphohistiocytosis	Professor S Strobel, Dr M Layton, Dr J Pritchard.	King's College Hospital, ICH (London)
28	Congenital syphilis*	Dr A Nicoll, Dr T Lissauer	PHLS, St Mary's Hospital (London)
29	Munchausen syndrome by proxy/non accidental poisoning and suffocation	Professor J R Sibert, Professor S R Meadow, Dr P Davis, Dr R McClure	St James's University Hospital, University of Wales, Medical School
30-32	Haemophilus influenzae type b vaccination failure*	Dr P Heath, Dr M Slack, Professor R Moxon, Dr N Begg	PHLS, National Haemophilus Reference Laboratory
32-34	Vitamin K deficiency bleeding*	Dr A McNinch, Dr J Tripp	Royal Exeter & Devon Hospital
34-35	Congenital dislocation of the hip	Ms S Godward, Dr C Dezateux	ICH (London)
35-36	Biliary atresia*	Dr J P McKiernan, Dr D Kelly, Dr A Baker	Birmingham Children's Hospital, King's College Hospital

* Studies still actively being surveyed as of December 1994

7.1 AIDS and HIV

Background: For the purpose of surveillance it is necessary to monitor HIV infection as well as AIDS. Antibodies from mothers infected with HIV may persist for up to 18 months in their children, which limits the interpretation of positive HIV antibody tests in infancy. Follow up of HIV seropositive infants born to mothers with HIV infection is essential, and therefore the reporting definition includes children whose infection status is indeterminate.

In Europe between 15% and 20% of infants born to mothers infected with HIV will themselves be infected. Most infants infected vertically develop laboratory indicators and/or clinical signs related to HIV within 12 months although only about 25% meet the surveillance definition of AIDS by this age. Other possible means of transmission to children include contaminated blood products, injecting drug use, and sexual intercourse.

Objective: The surveillance of paediatric HIV infection and AIDS in the United Kingdom and the Irish Republic.

Case definition: Any child less than 16 years of age who has AIDS, is HIV antibody positive, or from whom HIV has been cultured, or in whom HIV antigen has been detected. This includes children born to women infected with HIV whose infection status is indeterminate.

Study duration: The survey began in June 1986; an end date has yet to be decided.

Analysis: By the end of January 1994, 729 HIV positive children had been notified through the BPSU; 522 reports had been confirmed, 101 were duplicates, and 78 were reporting errors. Confirmation of a further 28 reports is awaited.

Table 5 - HIV positive children notified through the BPSU (to end of January 1994)

Source of infection	AIDS cases (deaths)		Total HIV seropositive
Blood transfusion	10	(4)	18
Haemophilia	19	(15)	46
Child of HIV positive mother:			
Infected	104	(51)	183
Indeterminate			87
Uninfected			188
TOTAL	133	(70)	522

We are aware of a further 235 children of mothers infected with HIV, and 221 children with haemophilia and 16 recipients of blood transfusion, who have not yet been notified through the BPSU. They have come to our attention either through the UK Haemophilia Centre, notification by obstetricians to the Royal College of Obstetricians and Gynaecologists, or through notification by paediatricians direct to the coordinating centre at the Institute of Child Health (London).

Children of indeterminate infection status are followed up to ascertain whether or not they are infected. Children with confirmed infection are followed up annually (or more frequently if they progress to AIDS), to monitor their clinical and immunological status.

Among vertically infected children, *Pneumocystis carinii* pneumonia (PCP) was the most frequently reported AIDS indicator disease at diagnosis, presenting in twenty-two of the 56 children with AIDS who were born in the British Isles. The onset of PCP was early (median age 4.1 months), and despite intensive treatment, the outcome was poor. Most children were not known to have been at risk of HIV infection until they presented with PCP.

The Paediatric European Network for Treatment of AIDS (PENTA) is continuing to enrol children in a trial to compare early versus deferred use of zidovudine (AZT) in children with mild or asymptomatic HIV disease (PENTA 1). One hundred and forty-eight children from 12 countries have entered the trial so far. The data and safety monitoring committee met recently and recommended that the trial should continue. A newsletter for families is available from the MRC HIV Clinical Trials Unit (Tel: 0171 351 8042). Paediatricians do not need to fill in BPSU follow up forms for children who are in the trial. The PENTA 3 trial is beginning: it will compare two drugs (AZT plus Dideoxycytinine, ddC with AZT alone) in children with symptoms. This study will examine tolerance and toxicity, and will run in parallel with a large efficacy study in adults (DELTA). Future multinational studies are planned to investigate how vertical transmission of HIV infection from mother to child may be reduced.

Paediatric HIV surveillance is coordinated at the Institute of Child Health in association with the Public Health Laboratory Service AIDS Centre at the Communicable Disease Surveillance Centre (Dr Angus Nicoll) and the Scottish Centre for Infection and Environmental Health (Dr David Goldberg).

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7.2 Reye's syndrome

Background: Surveillance of Reye's syndrome began in August 1981 as a venture shared between the BPA and the Communicable Disease Surveillance Centre (CDSC). Responsibility for case ascertainment transferred to the BPSU in June 1986. 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 obvious striking association with influenza and chickenpox, 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. Subsequently products that contain aspirin are required to carry warning labels.

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:

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

Study duration: This study began in June 1986; an end date has yet to be determined.

Analysis: Between August 1981 and July 1993 a total of 539 cases of Reye's syndrome were reported to the surveillance scheme, but the diagnosis was subsequently revised in 131 cases (24%). Trends in annual totals are shown in Table 6, overleaf. Eighteen reports were received in the year to July 1993, 16 of which had been followed up at the time of writing. Of these, the diagnosis in 10 had been subsequently revised and one other case did not meet the case definition.

Confirmed cases: year to July 1993: Two of the five cases were males and three were female. Their ages ranged from 5.2 months to 12.6 years (mean, 43 months; standard deviation 61.2; median 24.7 months). All cases lived in England and no seasonal distribution could be discerned because of the small number of cases. Two cases survived with no sequelae reported and two died, giving a case fatality rate of 40%, identical to that seen in 1991/92. One child survived with sequelae, but no details were given.

Three children were reported to have received medication before admission to hospital: one had received paracetamol; one cough mixture of unknown brand; and a 12 year old patient had been treated with "Disprin" for flu-like symptoms over a period of three days. Two children had past medical histories, but in neither case were the events compatible with an underlying metabolic disorder. One patient had a significant family history; a cousin who had died of an illness similar to Reye's syndrome in infancy/childhood.

Specific investigations for inherited metabolic disorders were undertaken in four of the five cases. Plasma amino acids, urine amino acids, and urine organic acids were assayed in three patients; urine orotic acids were measured in two; in one case a series of investigations was reported to be negative two months after admission, but no details of the investigations were given.

Revised diagnosis cases: Six of the ten cases whose diagnosis was subsequently revised were reported to have inherited metabolic disorders. Three cases had a possible fatty acid oxidation disorder, including twins diagnosed with a possible medium chain acyl CoA dehydrogenase deficiency (MCAD); one with an ornithine transcarbamylase deficiency (OTC); one with a disorder of the fructose pathway; and one with an unspecified inherited metabolic disorder. Mean and median ages of these patients were older than those reported in the previous year: mean 57.5 months; standard deviation 36.1; median 41.5 months (compared with mean 24.9 months; standard deviation 35.0; median 13.6 months in 1991/92). The four remaining cases were diagnosed, respectively, as Alpers disease, encephalopathy of unknown cause, overwhelming viral infection (organism not known), and sudden infant death syndrome.

Table 6 - Reye's syndrome surveillance 1981/82 - 1992/93

Reporting years (August-July)	Total reports from the British Isles	Revised diagnosis	Cases of Reye's syndrome	Number of Deaths (case fatality rate)
1981/82	47	7	40	26 (65)
1982/83	69	10	59	33 (56)
1983/84	93	12	81	36 (44)
1984/85	64	8	56	32 (57)
1985/86	53	13	40	22 (55)
1986/87	47	21	26	13 (50)
1987/88	44	12	32	19 (59)
1988/89	31+	12	18	9 (50)
1989/90	24+	8	15	7 (47)
1990/91	25	12	13	5 (38)
1991/92	24*	6	16	6 (40)
1992/93	18**	10	5	2 (40)
TOTAL	539	131	401	210 (52)

\+ Detailed information not available for one case.
* Follow up not yet received for two cases.
** Follow up not received for two cases and one case did not meet the case definition.

Comment:

The total number of reports to the surveillance scheme fell in the year to July 1993, with the lowest annual reported incidence of Reye's syndrome since surveillance began and a marked increase in the proportion of cases whose diagnosis was revised subsequently (Table 6). It is difficult to draw conclusions from such small numbers of cases, but the decline probably represents increasing awareness among paediatricians of inherited metabolic disorders in infants who present with an illness like Reye's syndrome. The gradual increase in the median age of cases from nine months in 1989/90 and 16.5 months in 1991/92 to 24.7 months in 1992/93 supports this explanation. Young patients are now more likely to be investigated for inherited metabolic disorders and an alternative diagnosis made. The increase in the median age of cases whose diagnosis was subsequently revised to a metabolic disorder may suggest that paediatricians are also investigating older children for inherited metabolic disease.

It was encouraging that no cases under 12 years had been exposed to aspirin before admission to hospital, although one 12 year old who subsequently died was treated with aspirin before admission.

It seems likely that small numbers of cases will continue to be reported. Six of the eight reports received by May 1994 have been followed up, of which one patient's diagnosis has been revised.

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7.3 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 10 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 has been estimated that 500 cases of necrotising enterocolitis in Britain each year could be attributed to exclusive formula feeding. These cases would account for at least 100 deaths and 150 laparotomies.

Objectives: 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 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: The study began in October 1993 and ended in October 1994.

Analysis: 179 cases were reported in the first five months. Cases were confirmed if one of the following criteria were met: gas in the bowel wall or portal tract, diagnosis confirmed at surgery, diagnosis confirmed at autopsy.

Seventeen of the 179 notifications were duplicates, four were considered not to be necrotising enterocolitis, for three the data was not retrievable, and 28 questionnaires have not yet been returned. Of the remaining 127 cases, 72 (57)% have been confirmed and 26 (20%) have died. The relationship to feeding practices has not yet been examined.

Paediatricians are asked to continue to report all suspected cases of neonatal necrotising enterocolitis, whether confirmatory features are present or not. We are most grateful for their participation.

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

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7.4 Congenital rubella

Background: In 1970 a national programme of immunisation against rubella was implemented with the aim of preventing congenital rubella. The National Congenital Rubella Surveillance Programme (NCRSP) was established in 1971 to monitor the effect of the immunisation programme. Selective immunisation of schoolgirls and adult women was supplemented in 1988 by the introduction of the combined measles/mumps/rubella (MMR) vaccine for all children in the second year of life. Although this policy has had considerable success, cases of rubella in pregnancy and congenital rubella still occur.

Objective: To determine the incidence of congenital rubella in Great Britain.

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

Study duration: Congenital rubella was included in the BPSU reporting scheme in January 1990. Notifications were made previously directly to the National Congenital Rubella Surveillance Programme (NCRSP). An end date has yet to be determined.

Analysis: Altogether 57 notifications have been made to the BPSU. Of these 27 are confirmed cases (Table 7), three are awaiting further information and the remainder were duplicates, notified in error, or were already known to the NCRSP from other sources. Other sources of reports include paediatricians, audiologists, virologists and CDSC. Eighty per cent of confirmed cases born since 1990 were first notified through the BPSU.

Table 7 - Cases of congenital rubella by year of birth and source of notification: 1987-1994

Year of birth	1987	1988	1989	1990	1991	1992	1993	1994	Total
BPSU	1	4	2	9	2	6*	2	1	27
Other sources	39	18	12	2	1	1	1	0	74
Total	40	22	14	11	3	7*	3	1	101

* Includes one set of triplets

Between January 1993 and June 1994, the NCRSP received 14 notifications from the BPSU. Five of these have been confirmed as cases of congenital rubella, but only four have been included in the registry figures as the fifth child was born abroad. Five of the remaining nine were duplicates, one was notified in error, one is still under investigation, and two had been notified previously from other sources.

Since 1988, when MMR vaccine was introduced for all children in the second year of life, congenital rubella has become a rare condition. Although the number of rubella infections in the community rose in 1993, so far there has been no increase in the number of registered cases of congenital rubella. The data for recent years is, however, provisional, as there is a time lag between maternal infection and the diagnosis and notification of a congenitally infected child.

It is essential that case ascertainment is as complete as possible, and reassuring when several clinicians notify the same case. Paediatricians are encouraged to notify to the BPSU all children suspected of having congenital rubella, whether or not they have the typical defects associated with congenital infection. We are very grateful for their cooperation.

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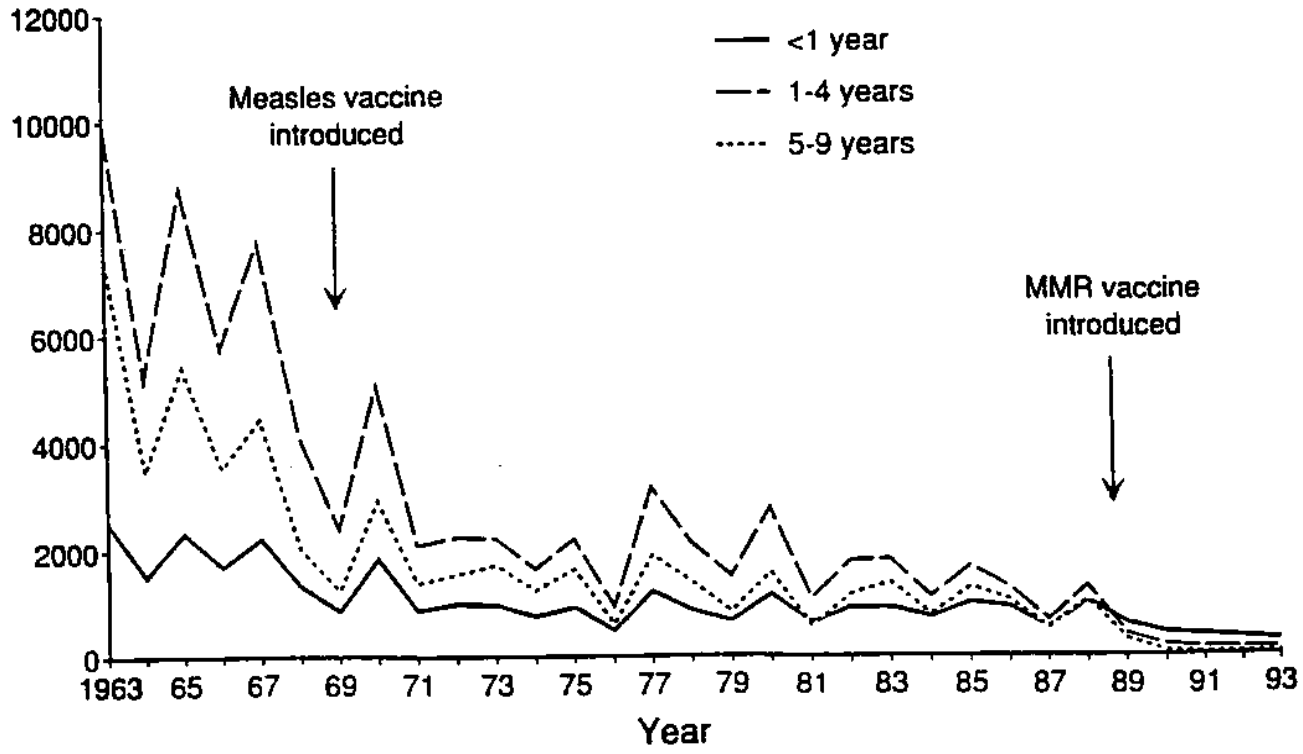
7.5 Subacute sclerosing panencephalitis

Background: Elimination of measles and its late complication, subacute sclerosing panencephalitis (SSPE) is the objective of the United Kingdom vaccination programme. Despite the introduction of measles vaccination in 1969 coverage with the single antigen vaccine was poor and the incidence of measles did not fall substantially until the measles, mumps, and rubella vaccine was introduced in October 1988 (Figure 3). Consequently, a clear reduction in SSPE incidence has not been seen, a low plateau has been maintained in recent years.

Objective: To monitor the incidence of SSPE.

Case definition: The criteria for SSPE are a typical history: usually of an insidious onset of mental deterioration, followed (usually within a few months) by motor dysfunction, progressive decerebration, and death;
and
raised measles antibody titres in the serum and cerobspinal fluid, typical electroencephalographic changes, and brain histology (when available).

Figure 3 - Annual Measles notification rates per 100,000 children under 10 years of age 1963-1993



Study duration: The study began in June 1986, following passive reporting to Communicable Disease Surveillance Centre (CDSC). The BPSU is no longer surveying this disorder, although passive surveillance to CDSC continues.

Analysis: The data for cases with onset since 1992 is not yet complete, but in the first six months of 1994, seven new cases have been reported. One 7 year old came from abroad, two have still to be confirmed, and the remaining four are 6, 9, 10, and 27 years old, respectively. Eight new cases were reported in 1993; five were not followed up as they were reported from the Republic of Ireland, Scotland, and Northern Ireland (this policy is presently being changed). The three from England were 8, 11, and 14 years old respectively.

Complete ascertainment of all cases is essential in order to show that when measles is eliminated, elimination of SSPE will follow. Consultant paediatricians and neurologists will be contacted personally by CDSC to request their cooperation in reporting all new patients seen - now that SSPE is no longer on the BPSU orange card - and an update to the 1992 report[1] will eventually be produced.

Reference: 1. Epidemiology of subacute sclerosing panencephalitis in England and Wales 1970-1989
Miller C, Farrington C P, Harbert K.
Int J of Epidemiol 1992; 21: 998-1006

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7.6 Juvenile dermatomyositis

Background: Juvenile dermatomyositis is a rare rheumatic disease of childhood which, because of its chronic course, is an important cause of disability. Little is known about its incidence in the United Kingdom but estimates from the United States suggest that 1-3.2 cases arise each year per million children. There have been reports of clustering of cases in the United States - but some clusters were in the spring and others in the autumn. Clinical experience suggests that the presentation varies between children, and that the mode of presentation and initial treatment may influence the ultimate prognosis.

Objectives: The aims of the BPSU surveillance were to estimate the incidence of juvenile dermatomyositis, look for clustering of cases in time and place, evaluate the presenting features, and the delay between onset and diagnosis, and document initial drug treatment. Respondents were sent a questionnaire and asked to provide demographic details of the children, the mode of presentation, and treatment of cases.

Case definition: Any child under 16 years of age with clinical evidence of symmetrical proximal muscle weakness and evidence of skin and soft tissue changes (for example, periorbital oedema, oedema in a shawl distribution, Gottron's papules, vasculitic ulcers, subungual capillary loops, soft tissue calcification). Supporting evidence comes from elevated creatine kinase and/or other muscle enzymes (which may be within the normal range); electromyographic abnormalities; abnormal muscle ultrasound; abnormal biopsy from muscle, skin, or other relevant tissue; other relevant abnormality, for example on magnetic resonance imaging

Study duration: This study began in June 1992. Consultants were asked to report any cases diagnosed after 1 January 1992; the study ended in December 1993.

Analysis: One hundred and twenty-one notifications were received. Forty-nine cases were confirmed, 40 in girls. Thirty-nine notifications were made in error (usually because the case had been diagnosed before 1 January 1992), 25 were duplicates, and eight questionnaires were not returned.

The data imply an annual incidence of 2.0 cases per million children (95% confidence interval 1.5-2.7), similar to that reported in the United States. The ratio of female to male cases was greater in the United Kingdom (4.4:1) than in the United States (2:1). Forty-three of the United Kingdom cases (88%) were Caucasian. The peak onset was in the summer months (May to July), and there was no evidence of geographical clustering. The mean age at onset was 7.9 years (range 1.5-15), and the mean time from onset to diagnosis was five months (range 0-16). The presenting features of the children are shown in Table 8.

Table 8 - Presenting features in 49 children with juvenile dermatomyositis

Presenting Features	Number	Percentage
Proximal muscle weakness	40	82
Muscle pain	20	41
Arthritis	8	16
Violaceous hue: face	31	63
Gottron's papules	15	31

Most were treated with oral corticosteroids either daily (67%) or on alternate days (12%). Only four patients (8%) received immunosuppressants initially. A follow up questionnaire is being sent to the consultants who reported confirmed cases and the results will be used to investigate clinical and therapeutic predictors of prognosis.

The BPSU survey enabled an estimate of the incidence of juvenile dermatomyositis in the United Kingdom to be made for the first time, and a picture to emerge of the presentation and treatment of the disease.

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7.7 Acute flaccid paralysis

Background: For a nation to gain a certificate of poliovirus eradication as part of the World Health Organisation's commitment to global eradication of polio by the year 2000, active clinical surveillance of suspected "wild" polio must be undertaken. In practical terms, this means being able to detect and investigate all cases of acute flaccid paralysis in children. There is a strong case for the establishment of a scheme in the United Kingdom and the Republic of Ireland. Although paralytic polio is a notifiable disease, less than half of all cases diagnosed in England and Wales between 1985 and 1990 were notified. Some cases were not detected until months, and occasionally years, after the acute illness. A request was made for all cases of acute flaccid paralysis to be reported, not only those in which polio was suspected.

Objectives: To measure the annual incidence of acute flaccid paralysis in children, and to determine its clinical features and whether the illness is caused by polio virus infection. If so, is the "wild" or vaccine-like virus responsible?

Case definition: In a child up to 16 years, acute onset of flaccid paralysis in one or more limbs or acute onset of bulbar paralysis. The differential diagnosis of acute flaccid paralysis includes paralytic polio, Guillain Barre syndrome, transverse myelitis, and traumatic neuritis.

Study duration: This study began in July 1991 and ended in June 1994.

Analysis: Cases were reported to the investigator by telephone in the first instance, to initiate timely laboratory investigations. **The single most important investigation is viral culture of faeces and at least two samples, taken 24 to 48 hours apart and within a week of onset of paralysis, were requested.**

One hundred and forty possible cases had been reported by the end of March 1994 (period of 31 months) 30 of which were duplicates or errors. A final diagnosis has been reached for 97 of the 110 cases confirmed to date. The commonest diagnosis was Guillain Barre syndrome (53 cases). Three cases of polio associated with vaccine were reported, consistent with previous estimates of the incidence of this condition. One imported case due to wild polio was detected. Other diagnoses include transverse myelitis, post-infectious neuropathy, and Bell's palsy.

Surveillance was maintained until July 1994. Several other countries have followed the BPSU initiative by establishing surveillance of acute flaccid paralysis. The newly formed British Neurological Surveillance Unit (BNSU) has included acute flaccid paralysis in adults as one of its reportable conditions.

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7.8 Androgen insensitivity syndrome

Background: Androgen insensitivity syndrome is a rare condition of childhood. In its complete form, affected individuals, are genetically male and produce male hormones but have normal female external genitalia. In its partial form, the external genitalia are abnormal: micropenis/clitoromegaly, bifid scrotum, perineoscrotal hypospadias.

Objectives: To determine the frequency complete androgen insensitivity syndrome occurs (annual incidence plus prevalence). To determine in such cases what proportion present as bilateral inguinal hernia in a female infant. To determine the frequency of partial androgen insensitivity syndrome. The survey also aims to provide information on associations between androgen insensitivity syndrome and other disorders, describe the range of phenotypic abnormalities in partial androgen insensitivity syndrome, and present optimal diagnostic procedures and management options.

Case definition: A child or infant under 16 years of age with a 46XY karyotype **and** with either:

1 normal female external genitalia (complete androgen insensitivity syndrome) **or**

2 abnormal external genitalia, consistent with the clinical phenotype of partial androgen insensitivity syndrome (micropenis, clitoromegaly, bifid scrotum, perineoscrotal hypospadias).

Study duration: The study began in September 1991 and ended in August 1993.

Analysis: During the two years of the study the BPSU was notified of 139 possible cases. Only a third (49) satisfied the criteria for androgen insensitivity syndrome: 29 for complete and 20 for partial. Twenty were excluded on grounds of age, five were duplicate notifications, and 36 have not yet been followed up. Most of the 23 diagnostic errors were associated with the phenotypic features of the partial syndrome; examples include testosterone biosynthetic defects, hypopituitarism, true hermaphroditism, Smith-Lemli-Opitz syndrome, Denys-Drash syndrome, hypospadias associated with multiple anomalies, testicular dysgenesis, and the Wilms's tumour, animdia, genitourinary abnormalities, mental retardation (WAGR) syndrome. A number of cases of XY gonadal dysgenesis were identified through the notifications and subsequent analyses of the follow up questionnaire. Samples of DNA from some of the patients have been sent to be analysed by Professor Goodfellow and colleagues in the Department of Genetics at the University of Cambridge in a study to identify genes that control early testicular differentiation.

Details of the 49 confirmed cases were presented in April 1994 to the British Society of Paediatric Endocrinology during the annual meeting of the British Paediatric Association. Table 9, overleaf, illustrates some of the clinical features that were identified.

The BPSU survey was confined to patients who were 16 years of age or younger at the time of the survey. The commonest mode of presentation of the complete syndrome was with inguinal hernias in apparent female infants. In clinical practice it is more common for a patient with the complete syndrome to present in later life with primary amenorrhoea. The diagnosis was established in four cases on the basis of a family history, usually an affected sibling. Gonadectomy must be performed in complete androgen insensitivity syndrome because of the risk of gonadal malignancy in later life. There is, however, no consensus about the optimal time for surgery. In this survey, most of the patients for whom precise information was available had undergone gonadectomy before puberty.

The genital abnormality in partial androgen insensitivity syndrome comprised severe (perineal) hypospadias in all cases, and was associated with micropenis in 15 cases. Five also had congenital anomalies elsewhere but no consistent pattern appeared. Twelve of the 20 cases were reared as males but no information is currently available on the consequences of this decision.

Table 9 - Clinical features of androgen insensitivity syndrome (AIS)

Clinical features of complete AIS (N=29)		Clinical features of partial AIS (N=20)	
Clinical presentation (number)		**Clinical presentation** (number)	
Inguinal hernia		**Genital abnormality**	
- bilateral	(22)	- Severe hypospadias	(20)
- unilateral	(14)	- Micropenis	(15)
Positive family history		**Associated congenital anomaly***	(5)
Other		**Sex rearing**	
- amniocentesis	(1)	- Male	
- karyotype for adoption	(1)	- Female	(12)
- unknown	(1)		(8)
Timing of gonadectomy			
Prepubertal	(16)		
Postpubertal	(7)		
Unknown	(6)		

* Includes coarctation of the aorta, microphthalmos and myopia, pyloric stenosis, chromosome translocation, mental handicap, and ectodermal dysplasia.

Conclusions

1 Standard texts suggest that one child in 64,000 is born with complete androgen insensitivity syndrome but the estimates are usually based on small studies. The BPSU survey does not make it possible to confirm or refute this figure.

2 The complete syndrome is relatively straightforward to diagnose, although an occasional case of pure XY gonadal dysengenesis was identified. This study suggests that gonadectomy is usually performed before puberty followed by oestrogen replacement at an appropriate age. Longer term studies are needed to determine the effect of this treatment strategy on the later development of osteoporosis.

3 Diagnosis of the partial syndrome remains a problem, as the clinical phenotype may be caused by numerous disorders. The diagnostic investigation should include an assessment of testosterone biosynthesis and metabolism, and biopsy of the testes at the time of surgery. The association with congenital anomalies and lower frequency of familial cases supports the heterogeneous nature of the partial syndrome.

4 It was surprising that most of the partial syndrome cases with severe genital anomalies were reared as males. It is important to learn about their development, particularly at the time of puberty and in later life with respect to potential fertility. Genetic and biochemical studies of the actions of androgen are currently in progress to develop in vitro tests to predict responsiveness to androgen.

5 Incidence and prevalence data for the partial syndrome are more difficult to obtain than for the complete syndrome from a retrospective survey because of diagnostic uncertainty. A prospective study is needed: a simple clinical criterion would be to notify births of all babies whose genital development was sufficiently abnormal to warrant an examination of the karyotype. The commonest cause (a 46XX female with congenital adrenal hyperplasia) can be excluded in due course by the use of reliable biochemical tests.

The principal investigator wishes to thank those paediatricians who reported cases and readily provided additional clinical information.

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7.9 Haemophagocytic lymphohistiocytosis

Background: The term haemophagocytic lymphohistiocytosis (HLH) includes the disease that was previously known as familial erythrophagocytic lymphohistiocytosis and cases associated with infection, including virus associated haemophagocytic syndrome. The distinction was misleading, cases with a likely genetic basis may not have a positive family history. Familial HLH can be triggered by infection including viruses.

Objectives:

1. Establish epidemiological data in the absence of other data from the United Kingdom (only one retrospective survey from Sweden has been reported).
2. Improve awareness and diagnosis. Although there is no diagnostic test, the syndrome is fairly easy to recognise if clinicians are of aware it.
3. Advice on management. The advent of bone marrow transplantation has made this disease potentially curable. The study coordinators have been able to advise on diagnosis and current management based on an increasing number of patient histories and contact with the reporting practitioners.
4. Research on aetiology and pathogenesis.

Case definition: <u>Clinical and Laboratory Criteria</u>

1. Fever for at least seven days;
2. Splenomegaly;
3. Cytopenia (affecting at least two of the three lineages in blood and not caused by a hypocellular/dysplastic bone marrow or malignant infiltration);
4. Hypertriglyceridaemia (fasting) and/or hypofibrinogenaemia;
5. Haemophagocytosis in bone marrow or spleen or lymph nodes with no evidence of malignancy.

Note: Haemophagocytic activity may not always be seen at the time of presentation and serial aspirates over time may be useful.

Exclusion Criteria

Previous immunosuppressive therapy, concurrent malignancy and Langerhans cell histiocytosis.

Study duration: This study began in September 1991 and ended in August 1994.

Analysis: During the first two years of the survey there were 66 notifications. Of these, 24 were duplicates. Of the remaining 42 patients reported 31 have been confirmed and 9 excluded by questionnaire and/or letter at the time of this report. The annual incidence for this 24 month period was approximately 1.31 cases/million children/year. This is similar to the figure obtained in a retrospective study in Sweden, (1.2 cases/million children/year).

Aetiology: HLH has a male to female ratio of 2:1, according to this study. The age at presentation ranged from 1 day to 15 years. Thirty-two per cent of patients had a family history of the condition, or occurred on a background of consanguinity suggesting a genetic base. Evidence of recent infection was found in 8 patients (about 40% of those in whom it was investigated). The infective agents includes Human herpes virus 6, respiratory synytal virus (RSV), Influenza A, Adeno virus, Epstein Barr virus (EBV) cytomegalovirus, mycoplasma and parvovirus B19.

Clinical and laboratory features: The onset was acute in 73% of patients. Fever occurred in 84%, hepatomegaly in 88%, bleeding in 65%, and splenomegaly in 80%.

Thrombocytopenia was found in 92%, anaemia in 88%, neutropenia in 79%. Almost all showed evidence of haemophagocytosis in marrow aspirates indicating the extent of marrow involvement. Haemophagocytosis was detected in the cerebrospinal fluid, trephine samples of bone marrow, liver, spleen, lymph nodes, and pleura. Forty-two per cent exhibited irritability and major signs in the central nervous system. Hyperlipidaemia was found in 85%, and hypofibrinogenaemia in 70%. The initial bone marrow aspirates of several patients were reported as normal but bone marrow aspirates gave a higher yield of diagnostic haemophagocytic infiltration than bone marrow trephines. Three cases were diagnosed pathologically at necropsy which emphasises that a high level of suspicion is needed to make the diagnosis. Pathological studies that are initially normal should be repeated, as findings may change during the course of the disease.

Treatment and outcome: Twenty-two patients received treatment, most commonly with a protocol including etoposide and prednisolone (more recently with dexamethasone), followed by cyclosporin. As neither treatment was curative, several patients received bone marrow transplantation. The overall mortality rate was 75%.

Future research: This study has helped to establish a network of clinical and basic research. Studies are underway to identify the underlying genetic susceptibility in a subgroup of those patients and will be reported after completion.

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7.10 Congenital syphilis

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

The importance to public health of this survey has increased since it began as suggestions have been made that antenatal screening for syphilis should cease[1]. 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 (220 new cases in GUM clinics in 1991 and 1992 in England). Moreover, the current levels of infection may not remain low indefinitely. In the United States, failure to provide universal antenatal care (including treponemal screening) has resulted in a substantial epidemic of congenital syphilis.

Objectives: Determine the minimum incidence of congenital syphilis in children, detect possible maternal and other factors, and look for trends while the study continues.

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

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

A **possible case** is one treated for syphilis who does not fill confirmed or presumptive criteria.

Study duration: This study commenced in July 1993 and is due to end in June 1996, subject to confirmation.

Analysis: In the first nine months of the survey six reports were made, all of these in the first two months. One was a 'presumptive' case, three were 'possible' and two were not confirmed when further information became available. Mothers of the four confirmed cases had evidence of previous infection with syphilis and they had been treated for infection. The low number may be explained in four ways, perhaps there are no cases to diagnose and report; secondly, there is a failure to make the diagnosis (especially for 'possible' cases without symptoms); thirdly, diagnosed cases may not be reported; fourthly, diagnosed cases may not see paediatricians (it is known that some are referred to specialists in genitourinary medicine with their mothers).

The research team is investigating the low number of reports through the BPSU scheme. The British Cooperative Clinical Group, a group of GUM physicians in the United Kingdom have begun a reporting scheme. The scheme is analogous to the BPSU, but reports are made quarterly. It is also looking for cases of treponemal infection (including syphilis) in pregnant women that require treatment, which will suggest how many infections are being detected by antenatal screening. Also routine reporting is began in 1994 from PHLS reference laboratories.

Reference: 1. Nicoll A, Moisley C. Antenatal screening for syphilis. *BMJ* 1994; **304**: 1253-4.

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7.11 Alleged Munchausen syndrome by proxy/non-accidental poisoning & suffocation

Background: The term "Munchausen syndrome by proxy" was first used in 1977 to describe illness or disability in a child, which is fabricated by another person (usually the mother) and causes the child to be presented persistently to doctors. The "illness" goes when the child is separated from the perpetrator. The more serious forms of such abuse include non-accidental poisoning and suffocation.

Non-accidental poisoning and suffocation of children are uncommon forms of child abuse. It is difficult to establish whether they are isolated events or merely one aspect of continuing child abuse that includes factitious illness and Munchausen syndrome by proxy.

Cases of Munchausen syndrome by proxy, non-accidental poisoning and non-accidental suffocation have been notifiable to the BPSU since September 1992. These forms of child abuse are unusual in that they are almost always first suspected by paediatricians themselves. Failure to recognise and act swiftly upon the diagnosis can have dire consequences for the child. Although the subject is topical choice because of the Beverley Allitt case, recognition of these forms of child abuse requires a high level of awareness and a knowledge of the common types of presentation. Several series of reports have been described by specialists in the field but, until now, there has been no prospective, population based study of the condition. This study aimed to fill this gap. A decision was made to include all three forms of abuse in one epidemiological study.

Objectives: To define the incidence and epidemiology of Munchausen syndrome by proxy, non-accidental poisoning and suffocation and to compare management and outcome of the different types of abuse in terms of management and outcome.

Case definition: The criterion for notification for any of the three specified conditions was that a formal child protection case conference should have been convened since September 1992 to consider a possible case. This conference must have been the first to consider the diagnosis in the child under discussion. After notification, the informer was asked to complete a questionnaire sent by one of the two research centres of Leeds or Cardiff; allocation was made geographically. The questionnaire, although detailed, usually took only a short time to complete.

Study duration: The study began in September 1992 and ended in August 1994.

Analysis: A good response was observed in terms of notifications and in the number of questionnaires completed and returned. The researchers are grateful for the cooperation of clinicians who participated.

We expect that our initial findings will be submitted for publication and presented early in 1995. In the meantime, please contact the following investigators with any queries: Dr Paul Davis on 01222 372451 for the south, western England and Wales and Dr Rob McClure on 0113 2433144 for northern, eastern England and Scotland.

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7.12 Invasive *Haemophilus influenzae* infection following Hib immunisation

Background: In the United Kingdom, prior to the introduction of active immunisation it was estimated that more than 1300 infants and young children suffered an episode of invasive *Haemophilius influenzae* b (Hib) disease every year. This included more than 900 cases of meningitis. It was estimated that more than 60 children die of this infection each year and that more than 100 were left with a neurological disability.

The BPSU included Hib after immunisation in its reporting system in September 1992 when immunisation of children less than 4 years old against Hib became part of the vaccination schedule in the United Kingdom and the Republic of Ireland. The data needed to assess the efficacy of Hib conjugate vaccines in Britain and Ireland do not yet exist. It is important therefore to establish a surveillance mechanism that will detect children who develop episodes of invasive Hib disease after immunisation.

Children are immunised at two, three, and four months of age. The duration of protection provided by the schedule is not known, but it is hoped that it is sufficient to avoid a need for booster immunisation in the second year of life. It is important therefore to maintain surveillance in children older than one year.

Paediatricians are asked to report cases immediately (by telephone) if *Haemophilus influenzae* is isolated from a normally sterile site from a child less than 10 years of age who has received at least one dose of the Hib vaccine. Attempts are made to collect acute and convalescent specimens of serum and the strain of *Haemophilus influenzae* is sent to the PHLS National Haemophilus Reference Laboratory at the John Radcliffe Hospital, Oxford to confirm its serotype.

Objectives: To identify the incidence of failure of Hib conjugate vaccine. In cases of vaccine failure: to identify the presenting illness and history of the patient, and to measure the serum concentration of anti-polyribosylribitol phosphate (PRP) antibody and look for a convalescent rise in antibody concentration.

Case definition: True failure of vaccine is defined as the occurrence of invasive disease after three doses of vaccine, or more than one week after two doses, in the first year of life, or more than two weeks after a single vaccination in a child above 12 months of age. Disease that occurs after vaccination has been given but before protection could reasonably be expected to develop constitutes an apparent failure of vaccine, that is, after one vaccination in the first year of life, within one week of the second vaccination in the first year, or within two weeks of a single vaccination in a child over 12 months of age.

Study duration: This study began in September 1992; an end date has yet to be set.

Analysis: Up to 1 April 1994, 100 notifications were made: 43 were from paediatricians, 35 from microbiologists, 21 from public health physicians, and one other. Sixteen were true vaccine failures, detailed in Table 10, overleaf, 48 were apparent vaccine failures, 16 were infected with non-capsulated strains of *Haemophilus influenzae*, and five of *Haemophilus influenzae* of other serotypes, the remaining 15 were not cases. Notifications have come from England (79), the Republic of Ireland (17), Northern Ireland (2), and Scotland (2). There have been no notifications from Wales.

Acute specimens for serology were available for only six cases of true vaccine failure. In all of those the concentration of anti-PRP antibody was less than 1 μg/ml (the level thought to correlate with long term protection). Convalescent serology was performed for 14 cases (at a median of 23 days after admission). A poor antibody response to disease (< 1 μg/ml) was noted in eight, five of whom had an associated medical condition. Thirty-nine of the 48 cases that met the definition for apparent vaccine failure had meningitis. Thirty-nine cases of apparent vaccine failure occurred after one dose

and one after two doses in the first year of life and eight followed a single dose in the second year of life. Acute serology performed on specimens from 14 of the 48 apparent cases revealed a concentration of antibody less than 1 μg/ml in 12 cases.

Sixteen cases of disease were affected with non-capsulated organisms: five had meningitis, a further five had epiglottitis, tracheitis or retropharyngeal abscess, and three had bacteraemia. Type f *Haemophilus influenzae* was responsible for four of the five other infections with encapsulated organisms.

Table 10 - Clinical details of true vaccine failures

Cases	Hib vaccination(s) given at age (months)	Age of onset of disease (months)	Diagnosis	Associated conditions*
1	2/3/4	11	Orbital cellulitis	-
2	2/4	6	Meningitis	Premature (28 weeks)
3	2/3/5	11	Meningitis	-
4	2/3/4	12	Meningitis	-
5	2/3/4	12	Meningitis	Premature (29 weeks) Low IgG/M/A
6	2/3/5	5	Meningitis	Premature (35 weeks)
7	2/3/4	14	Meningitis	-
8	3/5	7	Meningitis	Congenital microcephaly
9	2/3/4	11	Pneumonia	Down's syndrome
10	3/5/6	14	Pneumonia	-
11	15	16	Meningitis	-
12	16	26	Meningitis	-
13	13	23	Epiglottitis	Down's syndrome
14+	19	24	Meningitis	Premature (32 weeks)
15	16	26	Epiglottitis	Premature (32 weeks) Low IgG/A
16	19	29	Bacteraemia	Chromosomal abnormality (duplication 12p)

* Associated conditions that may predispose to infection and/or poorer response to immunisation

** All cases reside in England apart from case 10 (Scotland) and cases 12 and 16 (Republic of Ireland)

\+ Case 14 died

Comment

The introduction of Hib conjugate vaccine has resulted in a dramatic fall in the incidence of Hib infection in the United Kingdom. Reports from England and Wales received by CDSC indicate a 95% fall in laboratory isolates in the 1 to 4 year age group. However, there is no room for complacency as the duration of protection from immunisation at two three and four months is not certain. A second year booster is not provided, (in contrast to the schedules in some countries). There may also be subgroups who are at greater risk for vaccine failure for example, premature infants and infants with Down's syndrome.

It is also possible that *Haemophilus influenzae* of types other than b may replace type b as a cause of invasive disease in children. There is as yet no evidence to support this concern, but it is vital to continue active surveillance and identification, including serotyping, of strains that cause invasive disease. Most recent isolates causing invasive disease have in fact been non-capsulated strains. Early telephone reporting ensures that appropriate specimens are collected and enable the paediatricians to receive prompt feedback.

We are most grateful for the collaboration of paediatricians and microbiologists in this study.

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7.13 Vitamin K deficiency bleeding

Background: One of the first conditions to be studied through the BPSU network was vitamin K deficiency bleeding, which was then known as "Haemorrhagic disease of the newborn". The new term is now preferred as it is more informative and does not imply misleadingly that the condition is confined to newborn babies. The BPSU survey found 25 confirmed and two probable cases in the British Isles in the two year period from March 1988 to February 1990[1]. At that time at least 60% of newborn babies received prophylaxis with intramuscular vitamin K and 13% received no prophylaxis. Twenty of the 27 cases reported had received no prophylaxis, seven had received a single oral dose of vitamin K (Konakion (Roche)) at birth, and no cases had definitely received intramuscular prophylaxis.

The trend towards oral rather than intramuscular prophylaxis was encouraged by reports[2,3] suggesting that intramuscular vitamin K might double the risk of subsequent malignancy. Subsequent studies[4] have failed to confirm such a risk but in 1993 a national survey of prophylaxis policies (John Barton and colleagues, unpublished observations) showed that some 60% of babies were receiving oral prophylaxis, 35% intramuscular prophylaxis, and 5% none. Most maternity units that used oral prophylaxis routinely offered multiple doses as recommended by a working party of the British Paediatric Association[5]. The rationale for repeated oral doses is that when bleeding occurs after a single oral dose at birth its onset is at least delayed; doses repeated at intervals should therefore "repeatedly delay" the onset of bleeding throughout the period of risk.

A second BPSU survey of vitamin K deficiency bleeding began in January 1993 to monitor the efficacy of current prophylaxis regimens.

Objectives: To re-evaluate the incidence and epidemiology of vitamin K deficiency bleeding.

Case definition: Any infant under six months of age with spontaneous bruising/bleeding or intracranial haemorrhage associated with prolonged clotting times, not due to an inherited coagulopathy or disseminated intravascular coagulation.

Study duration: The study began in January 1993 and is due to end in December 1994.

Analysis: In the first 18 months of the second survey 74 notifications have been made; 33 questionnaires have been returned so far, from which 14 confirmed and three probable cases have been identified, the details of which are shown in Table 11. Two cases were reported in error and 14 were duplicate reports.

If the accrual rate of the 1988-90 survey (27 confirmed/probable cases in 24 months) were to be sustained in the current survey we would expect 20 confirmed/probable cases in the first 18 months. As about 60% of the notifications have yet to be classified (questionnaires have not yet been returned) the current total of 17 confirmed/probable cases is likely to exceed the 'expected' total, suggesting that the incidence of vitamin K deficiency bleeding may have risen since the first survey.

Table 11 - Details of 17 probable/confirmed cases of vitamin K deficiency bleeding

Features	Number
Late onset (after 7 days)	13
Wholly breast-fed	3
Liver disease	5 (anti-trypsin deficiency 2, biliary atresia 2, unspecified 1)
Received oral vitamin K prophylaxis	8
No vitamin K prophylaxis	9 (parental consent withheld in 3 cases)
Intracranial haemorrhage	5 (4 received oral vitamin K, 1 received no prophylaxis, 3 had liver disease

Five of the eight babies who bled in spite of oral prophylaxis had liver disease and another was failing to thrive because of pancreatic dysfunction. One baby had normal liver function, and another was not tested. Six babies received a single dose of oral vitamin K at birth. In five cases a 1mg dose was used; in one case the dose was not specified. One baby received 2mg on both the first and second day of life and bled at 46 days. It is not known what dose was given to the baby who had anti-trypsin deficiency and presented at 42 days with an intracranial haemorrhage, nor whether repeat doses were given.

Conclusions:

The major risk factors for vitamin K deficiency bleeding breast feeding and unrecognised liver disease are again confirmed. Compared with the first survey, a larger proportion of the babies bled after oral vitamin K and a smaller proportion had received no prophylaxis, reflecting changes in prophylaxis policies. Neither in the first survey, nor so far in the second, has a single case of vitamin K deficiency bleeding followed prophylaxis with intramuscular vitamin K. To date we have not been notified of bleeding after repeated oral doses as are recommended by the BPA working party but this has been described in Germany[6]. Lack of a licensed oral preparation of vitamin K for use in babies and the difficulties of administering multiple doses continue to cause concern[7].

References

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7 Croucher C, Azzopardi D. Compliance with recommendations for giving Vitamin K to newborn infants. *BMJ* 1994; **308**: 894-895

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7.14 Congenital dislocation of the hip

Background: Congenital dislocation of the hip (CDH) is a common and potentially disabling deformation. The screening programme currently used in the United Kingdom was introduced without prior evaluation. It aims to identify presymptomatic cases by clinical examination, when splinting in abduction may avoid the need for surgery. The effectiveness of this programme has been questioned, as cases not detected by screening continue to occur. Furthermore, the number of infants treated as a result of positive screening tests exceeds the number that would be expected to be treated for established dislocation in the absence of screening. This suggests that the test may have a high false positive rate. Screening by ultrasound examination has been proposed as a more effective alternative, but this method requires formal evaluation.

Objectives: To identify the number of infants (per 1000 live births) who receive treatment for CDH as a result of a positive screening test. To identify the number of infants and young children (per 1000 total population) who undergo an operative procedure for CDH, in whom CDH had not been detected by screening. To identify the range and variability of existing screening practices for CDH in the UK.

Case definition: Congenital dislocation of the hip is defined as 'a deformation of the hip joint present at birth, in which the head of the femur is, or may be, partly or completely displaced from the acetabulum. This includes secondary hip joint dysplasia whether or not hip instability or dislocation persists'[1].

Study duration: The BPSU part of this study began in April 1993 and ended in July 1993.

Analysis: Paediatricians and orthopaedic surgeons were asked to report the number of cases of congenital dislocation of the hip (CDH) first treated with abduction splinting for each month from April to July 1993. Orthopaedic surgeons also reported operative cases on a monthly green card, from April 1993 to April 1994, through a similar surveillance scheme established through the British Orthopaedic Association (BOA). The average monthly response rate for BOA respondents was 90%, which compares favourably with the BPSU figures for this period. A total of 951 cases was reported, 344 (36%) by paediatricians. Of these, 230 (67%) are currently known to fit the case definition, while 48 (14%) did not and 66 (29%) cases have yet to be confirmed. The data in this report are therefore preliminary. Duplicate reporting has been minimised in most centres by good liaison between paediatricians and surgeons, two children reported by paediatricians were subsequently reported by orthopaedic surgeons. Please return any outstanding questionnaires to the study investigators as soon as possible.

Orthopaedic surgeons reported first operative procedures on cases of CDH for the year ending April 1994; data from Hospital Episode System (HES) will be used to validate the reports in at least two regions. The preliminary findings of the BPSU/BOA surveillance study have been used already in the design of a multicentre trial of the role of ultrasound in the management of clinically detected instability of the neonatal hip, which is being coordinated by the Perinatal Trials Service in Oxford (further information from Lesley Morgan, the Hip Trial Coordinator, Tel: 01865 311700).

Final reports of the surveillance study and the related survey of screening and management of CDH will be available in 1995, and a short summary will be circulated to all respondents from the BPSU and BOA.

The study investigators would like to thank all the paediatricians and orthopaedic surgeons who have participated in the surveillance study and the screening and management survey.

Reference: 1. Dunn PM. Screening for congenital dislocation of the hip. In: MacFarlane JA, editor. *Progress in child health*, Volume 3. Edinburgh: Churchill Livingstone, 1987: 1-13.

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7.15 Biliary atresia

Background: Biliary atresia is an uncommon disease of infancy, which is fatal if not treated. It is the commonest cause of liver disease in children of such severity as to require liver transplantation. The aetiology is unknown and incidence of the condition in the United Kingdom and the Republic of Ireland are unknown.

Objectives: The BPSU survey seeks to answer the following questions. What is the national incidence of biliary atresia? Are there any recognisable aetiological features? What is the current pattern of referral and why is referral delayed? What is the outcome for affected children following modern management and how many will eventually need liver transplants?

Case definition: Notification is requested of patients with conjugated hyperbilirubinaemia, bilirubinaemia, pale stools, **and** in whom biliary atresia is a possible diagnosis at the time of reporting.

Study duration: This study began in March 1993 and is due to end in February 1995.

Analysis: The study has received a positive response from paediatricians, paediatric surgeons, pathologists, and general practitioners. It seems likely for two reasons that most or all cases of biliary atresia are being reported. Firstly, many cases have been notified by multiple sources. Secondly, many paediatricians have notified suspected cases in whom an alternative diagnosis has eventually been made.

To July 1994, 52 cases have been confirmed, and a few cases remain about whom we await details. Ten centres undertook surgery for these children, but only three centres saw more than two children during the year. The mean age at which surgery is undertaken has fallen compared with previous surveys, although avoidable delays may have occurred in some cases.

The study is now moving into its second phase, in which the cases will be followed for a number of years to determine the medium and longer term outcome. Questionnaires have already been sent to the notifying paediatricians for the first year follow up.

The investigators wish to thank all those who have notified cases and completed questionnaires.

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8 New studies for 1994

Three new studies have so far been introduced in 1994, they are as follows:

8.1 Medium chain acyl CoA dehydrogenase deficiency

Background: This is an inborn error of fatty acid oxidation which has 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 remain asymptomatic. The sudden and unexpected death of some may be attributed to sudden infant death syndrome. Studies of the frequency of the common mutation in heterozygotes suggest that medium chain acyl CoA dehydrogenase deficiency (MCAD) is relatively common, with a birth prevalence of about one in 10,000. It seems, however, that less than 50% of these are diagnosed clinically.

Objectives: To identify all patients in the United Kingdom and the Republic of Ireland. To provide data to inform decisions about whether to include MCAD in a neonatal screening programme. It is hoped that the management of individual patients and their families will benefit.

Case definition: Through an accepted laboratory criterion.

Study duration: The study began in March 1994 and is due to end in February 1996.

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8.2 Adverse neonatal outcomes of delivery or labour in water

Background: The National Epidemiology Unit in Oxford, is conducting a survey in England and Wales of the use of water during labour and delivery. Preliminary reports suggest that facilities are becoming widely available and that several thousand deliveries took place in water in 1993. There is little evidence that properly managed delivery in water puts babies at risk, although the overall safety of labour or delivery in water has not been evaluated. Delivery in water may be restricted to women who are perceived to be at low risk of having an adverse outcome, but the increasing use of water during labour and delivery means that adverse outcomes will occur. Definitions of low risk and guidelines about what is safe practice vary for example, in terms of care of the pool, water temperature, and management of the third stage. There have been several reports of perinatal death or damage following, though not necessarily caused by, labour or delivery in water. Local policies are being developed or revised in response to these anecdotal reports. There is an urgent need to establish whether the use of water increases risk, so that health authorities can formulate local policy on the basis of reliable data, and maintain professional and public support.

Objectives: The study aims to estimate the incidence of adverse neonatal outcomes in babies delivered in water: and identify babies who are admitted to special care units or die following labour in water, to determine whether the use of water during labour is associated with adverse outcomes. Valid estimates for comparison of adverse outcome in women of low risk are not available, and an important element of this study, with potential for wider application, will be the determination of appropriate comparison rates from existing sources of data.

Case definition: Any perinatal death following delivery in water or following labour in water. Any admission to special care unit within 48 hours of birth following delivery or labour in water.

Study duration: The study began in April 1994 and is due to end in March 1995.

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8.3 Transient and permanent neonatal diabetes

Background: Neonatal diabetes is rare. In the British Diabetic Association register of childhood diabetes (the transient form not included) only 14 cases were reported over the 10 year period. There is no published incidence for transient neonatal diabetes.

In permanent neonatal diabetes the dependence on insulin treatment persists throughout life. In transient neonatal diabetes insulin dependence has (by conventional definition) resolved by one year of age (mean two months). The transient form presents in infants born at term but small for dates, within the first six weeks of life. Response to insulin is dramatic, and within weeks, or months the condition resolves. It has been proposed that the defect is due to a delay in beta cell maturation.

This study of patients with transient neonatal diabetes will test whether HLA type and autoantibody production in children with transient neonatal diabetes who later develop diabetes mellitus are atypical of classical Type I diabetes. If this is established it will suggest that these cases have a pathological basis similar to defects seen in Type II diabetes. The study will also provide a longterm model of the influence of perinatal beta cell dysmaturity on the later onset of type I and II diabetes. More generally, it will define the growth and development of such children.

Objectives: To establish the incidence of both the transient and permanent forms of neonatal diabetes. The clinical, physiological, and genetic characteristics of children who present with these two conditions will be studied. The study will provide a unique cohort of cases, in which the investigators hope to evaluate prospectively the influence of neonatal pancreatic islet dysfunction on later physical and endocrine development.

Case definition: Neonatal onset diabetes: all infants of 37 weeks gestation or older who develop persistent hyperglycaemia requiring insulin treatment within the first six postnatal weeks. Transient neonatal onset diabetes: those who become non-insulin dependent within the first year of life. Permanent neonatal onset diabetes: those in whom the requirement for insulin treatment is still present at the age of one year (and by inference will be permanent).

Study duration: This study began in July 1994 and is due to end in June 1995.

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9 International Developments

One of the successes of the BPSU has been in its ability to transplant the unit's methodology to other countries. Several countries have developed 'active' systems of paediatric surveillance to monitor rare disorders, along similar lines to the BPSU's system.

Following a meeting in 1990 of the Union of National European Societies and Associations (UNEPSA), a working party was set up in order to establish a network of paediatric surveillance units. German and Dutch units have subsequently been developed. The national units have developed a close liaison and several studies are being conducted in the three units simultaneously, using similar research protocols to produce a larger pool of data for analysis. An application for the funding of a 'European Paediatric Surveillance Unit' has yet to be approved by the European Community .

German Paediatric Surveillance Unit

A German surveillance scheme was set up in July 1992. Several problems had to be solved in the application of the BPSU model to the German systems of hospital care for children. No register of consultants existed that was equivalent to that held by the BPA. No national system of laboratory reporting is yet in place to enable diagnoses to be validated, and information about cases in the former German Democratic Republic can be difficult to obtain. Progress is being made, however, and the response rate (greater than 75% since February 1993) has risen to over 85% since August 1993.

The system began with five conditions (diabetes in under fives, Reye's syndrome, neonatal thrombosis, Ondine's curse (primary failure of respiratory regulation), and systemic *Haemophilus influenzae* b (Hib) infections). It has been extended to include acute renal failure, Kawasaki disease, haemolytic disease of the newborn, and complications of pertussis infection.

Preliminary results of the studies on Hib, diabetes, Ondine's curse, and acute renal failure were presented at the annual meeting of the German Paediatric Society.

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Dutch Paediatric Surveillance Unit

The Dutch unit started work in October 1992. The Dutch Paediatric Society had given its approval in November 1990 and financial support for 1992 and 1993 had been obtained from the Ministry of Health. About 245 paediatricians in general hospitals receive the monthly report card. In the eight university hospitals a specific contact person has been nominated for each disorder, and is responsible for the reporting of all cases in that hospital. Non-responders receive a reminder letter with the monthly report cards. Five disorders were listed initially: coeliac disease, vitamin K deficiency bleeding, acute flaccid paralysis, sickle cell disease, and thalassaemia major. In January 1994 three more studies were added: diabetes mellitus, neural tube defects, and *Haemophilus influenzae* b disease.

The overall response rate in the first three months was 81%; by the end of 1993 it had risen to 90%, and systematic failure to respond is rare. Specific research groups are confirming the notifications that have been received, adding information acquired through postal questionnaires and interviews.

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Australian Paediatric Surveillance Unit (APSU)

The APSU began active monthly surveillance in May 1993 following its official launch during a scientific meeting of the Australian College of Paediatrics. About 1,000 paediatricians and clinicians who deal specifically with children receive monthly report cards that list eight rare disorders: drowning/near drowning; extrahepatic biliary atresia; haemorrhagic disease of the newborn (vitamin K deficiency bleeding); HIV/AIDS; congenital rubella; Kawasaki disease; Rett syndrome, and childhood dementia. The overall response rate in the first six months was about 80%. In states such as New South Wales where a reminder letter has been sent to non-responders, the response rate reached 90%.

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Malaysian Paediatric Surveillance Unit (MPSU)

The MPSU was set up in December 1993 and officially launched in June 1994. Its aims and objectives are based on those of the BPSU. The MPSU will complement disease surveillance carried out by the Malaysian Ministry of Health.

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MPA Secretariat, Institut Pedatrik, Hospital Kuala Lumpur, 5074 Kuala Lumpur, Malaysia

Canada and Turkey are also considering the development of a surveillance unit on the lines of the BPSU. In both instances the BPSU is advising on their development.

10 Completed Studies

The BPSU has now completed 18 studies. Information about these studies has been included in previous BPSU Annual Reports, which are available from the BPSU office. The studies and their principal investigators are listed below.

1 X-linked anhydrotic ectodermal dysplasia (June 1986 - August 1986)
Dr A Clarke, University Hospital, Heath Park, Cardiff, CF4 4XW.

2 Lowe syndrome (June 1986 - February 1988), Dr C McKeown
Department of Medical Genetics, St Mary's Hospital, Manchester 13 OJH.

3 Insulin dependent diabetes in under fifteens (January 1988 - December 1988)
Professor J D Baum, Institute of Child Health, Royal Hospital for Sick Children, Bristol.

4 Drowning and near drowning (January 1988 - December 1989)
Professor J Sibert Department of Child Health, Llandough Hospital, Penarth,
South Glamorgan CT6 1X.

5 Higher order births (January 1989 - December 1989)
Professor M Levene, Leeds General Infirmary, Belmont Grove, Leeds LS2 9NS.

6 Haemorrhagic disease of the newborn (March 1988 - February 1990)
Dr A W McNinch, Dr H Tripp, Department of Child Health, Royal Devon & Exeter Hospital, Barrack Road, Exeter EX2 5DW.

7 Haemorrhagic shock encephalopathy syndrome (June 1986 - December 1988)
Dr S Hall c/o PHLS Communicable Disease Surveillance Centre, 61 Colindale Avenue,
London NE9 5EQ.

8 Haemolytic uraemic syndrome (June 1986 - December 1989)
Dr S Hall (see 7 for address)

9 Kawasaki disease (June 1986 - December 1992)
Dr S Hall (see 7 for address)

10 Congenital toxoplasmosis (June 1989 - May 1990)
Dr S Hall (see 7 for address)

11 Acute rheumatic fever (January 1990 - December 1990)
Dr C Boyd-Scobie, Dr S Hall (see 7 for address)

12 Rett syndrome (April 1990 - June 1990)
Dr A Kerr, Quarrier's Homes, Bridge of Weir, Renfrewshire, PA1 3SA.

13 Measles, Mumps, Rubella-Meningococal meningitis (Jan 1990 - Dec 1991)
Dr N Begg, PHLS Communicable Disease Surveillance Centre, 61 Colindale Avenue,
London, NW9 5EQ.

14 Neonatal herpes (June 1986 - Dec 1991)
Ms P A Tookey, Professor C S Peckham, Dr R Dinwiddie, Unit of Epidemiology and Biostatistics, Institute of Child Health, 30 Guilford Street, London WC1N 1EH.

15 Chemistry set poisoning (Jan 1991 - April 1992)
Dr E Mucklow, St Mary's Hospital, Newport, Isle of Wight PO30 5TG.

16 Galactosaemia (Jan 1988 - Sept 1991)
Mrs A Green, Dr J Holton, Dr M Honeyman*, Professor J Leonard
*The Child and Family Centre, 142 Maas Road, Northfield, Birmingham B31 2PR.

17 Long term parenteral nutrition (Feb 1992 - April 1992)
Professor D Candy, Professor E Ross, Dr S Devane
Department of Child Health and Community Paediatrics
King's College School of Medicine and Dentistry, London SE5 8RX.

18 Insulin dependent diabetes (Jan 1992 - Dec 1992)
Professor J D Baum, Ms E Wadsworth, Institute of Child Health, Royal Hospital for Sick Children, St Michael's Hill, Bristol BS2 8BJ.

11 Publications 1993-1994

Reye's syndrome in the British Isles: report for 1990/91 and the first decade of surveillance Newton L, Hall S M, *Communicable Disease Report*, 1993; **3** R11-6.

The British Paediatric Surveillance Unit. Hall S M, Roberts C. *Bulletin of the Royal College of Pathologists 1993*; **82**: 12-7.

Rubella surveillance to December 1992: second joint report from the PHLS and the National Rubella Surveillance Programme. Miller E, Waight P A, Vurdien J E, Jones G, Tookey P A, Peckham C S. *Communicable Disease Report* 1993, **3**.

Haemophilus influenzae type b. Booy R, Moxon E R. *Arch Dis Child* 1993, **68**, 440-1.

Vertically transmitted HIV infection in the British Isles. Ades A E, Davison C, Holland F J, Gibb D M, Hudson C N, Nicoll A, Goldberg D, Peckham C S. *BMJ*. 1993; **306**: 1296-9.

Kawasaki disease in the British Isles. A survey of management. Dhillon R, Newton L, Rudd P, Hall S M. *Arch Dis Child* 1993 **69**: 631-8.

Galactosaemia, Results of the British Paediatric Surveillance Study 1988-90. Honeyman M M, Green A, Holton J B, Leonard J V. *Arch Dis Child* 1993; **69**: 339-341.

Screening for toxoplasmosis during pregnancy. Peckham C, Logan S. *Arch Dis Child* 1993; **68**: 3-5.

The epidemiology of subacute sclerosing panencephalitis in England and Wales 1970-1989. Miller C, Farrington C P, Harbert K. *In J Epidemiol* 1993: **21**: 998-1006.

Accidents and child abuse in bathtub submersions. Kemp A M, Mott A M, Sibert J R. *Arch Dis Child* 1994 **70**: 435-458.

12 Presentations of BPSU studies 1993-94

BPA Annual Scientific Meeting 1993

Kawasaki disease in the British Isles: the first decade of surveillance
Dr Susan Hall (BPSU and PHLS Communicable Disease Surveillance Centre, London).

Survey of children on long term parenteral nutrition, UK and Eire, 1992
Dr S P Devane (Department of Child Health, King's College School of Medicine and Dentistry and the BPSU, London).

Changing clinical pattern of Reye's syndrome in the British Isles 1982-1990
Dr R Hardie. (BPSU and PHLS Communicable Disease Surveillance Centre, London).

Haemophagocytic lymphohistiocytosis: first results of a prospective national survey
Dr P Heney (St James's University Hospital, Leeds).

BPA Annual Scientific Meeting 1994

Neonatal herpes surveillance 1986-1991
Ms P A Tookey (Institute of Child Health, London).

Androgen insensitivity syndrome; diagnostic yield in the complete and partial forms.
Dr Y Teoh, Dr M N Patterson, Professor A I Hughes (Department of Paediatrics, University of Cambridge).

Estimation of BPSU study ascertainment rate using a statistical capture recapture technique
Ms E Wadsworth, Dr J P Shield, Mr R Lynn, Professor J D Baum. (Institute of Child Health, Bristol; BPSU, London).

13 Support groups for current and recent conditions on the BPSU card

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, 59 Corporation Road, Darlington, Co. Durham, DL3 6AD.

Galactosaemia
Galactosaemia Support Group, Mrs S Bevington 18 Nuthurst, off Reddicap Heath Rd,
Sutton Coldfield, W Midlands B75.

Guillain-Barre Syndrome
Guillain-Barre Syndrome Support Group,'Foxley', Holdingham, Sleaford, Lincolnshire, NG34 8NR.

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, Bell Close, West End Road, Ruislip, Middlesex HA4 6LP.

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.

14 Contact addresses

Ms R Abbott, Infant and Child Nutrition Group, MRC Dunn Nutrition Unit, Downham's Lane, Cambridge CB4 1XJ

Dr A E Ades, Department of Epidemiology, Institute of Child Health, London WC1N 1EH

Arthritis and Rheumatism Council, Copeman House, St Mary's Court. St Mary's Gate, Chesterfield, Derbyshire S41 7TD

Dr A Baker, King's College Hospital, Denmark Hill, London SE5 8RX

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

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

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

Dr R Booy, St Mary's Hospital, Praed Street, London WC1

Ms B Botting, Office of Population Censuses & Surveys, St Catherine's House, Kingsway, London WC2 6JP

British Neurological Surveillance Unit, Chalfont Centre for Epilepsy, Chalfont St. Peter, Bucks SL9 0RJ

British Paediatric Association, 5 St Andrews Place, Regent's Park, London NW1 4LB

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

Professor D Candy, Department of Child Health and Community Paediatrics, King's College School of Medicine and Dentistry, London SE5 8RX

Dr M Catchpole, PHLS Communicable Disease Surveillance Centre, 61 Colindale Avenue, London NW9 5EQ

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

Dr R R Counahan (BPSU Irish Representative), Paediatric Department, Regional Hospital, Waterford, Republic of Ireland

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

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

Dr S Devane, Department of Child Health and Community Paediatrics, King's College School of Medicine and Dentistry, London SE5 8RX

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

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

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

Dr E Elliot, Australian Paediatric Surveillance Unit, PO Box 34, Camperdown, NSW 2050 Australia

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

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

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

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

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Dr P Heney, c/o St James's University Hospital, Leeds LS9 7TF

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Dr D Kelly, The Children's Hospital, Ladywood Middleway, Birmingham B16 8ET

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

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

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

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

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Dr C McKeown, Department of Medical Genetics, St Mary's Hospital, Manchester M13 OJH

Dr J P McKiernan, The Children's Hospital, Ladywood Middleway, Birmingham B16 8ET

Dr A McNinch, Department of Child Health, Postgraduate Medical School, Royal Devon & Exeter Hospital, Barrack Road, Exeter, EX2 5DW

Professor S R Meadow, Department of Paediatrics and Child Health, St James's University Hospital, Leeds LS9 7TF

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

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Royal College of Physicians (Ireland), Faculty of Paediatrics, 6 Kildare Street, Dublin 2

Dr P T Rudd, Children's Centre, Royal United Hospital, Bath BA1 3NG

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

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