Royal College of Paediatrics and Child Health
British Paediatric Surveillance Unit

17th Annual Report, 2002-2003

BPSU

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on the work of the Unit and takes every effort to respond positively.

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British Paediatric Surveillance Unit – Annual Report 2002-2003

Compiled and edited by Richard Lynn, Hilary Kirkbride, Mike Preece, and Jugnoo Rahi, September 2003

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* Retired in 2002

\# Retired July 2003

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Foreword

This has been another year of change, particularly because Professor Catherine Peckham retired and left the Executive Committee in March. Catherine was a founder member of the BPSU in 1986, chair for 3 years in the 1990's and has been a loyal and industrious member of the Committee ever since; I have no doubt that her wise council will be missed. She is replaced on the Committee by Professor Carol Dezateux who has also succeeded Catherine as Head of the Centre for Paediatric Epidemiology and Biostatistics at the Institute of Child Health.

Other changes on the Committee have also occurred: Jugnoo Rahi, who has been Medical Adviser on non-infectious disease projects for 4 years leaves this summer to be succeeded by Rachel Knowles who is a trainee in paediatric epidemiology. A welcome addition is Hugh Davies, a DGH paediatrician, who has had the valuable experience of Chairing the London Multicentre Research Ethics Committee for five years and remains involved with the Central Office of Research Ethics Committees. With the increasing complexity of ethics review his input will be most valuable. I would also like to take the opportunity to congratulate Chris Verity, my predecessor as Chairman, who has now been appointed Chairman of the Academic Board of the RCPCH and also Angus Nicoll on his award of the CBE in the New Year Honours List.

In the past year a number of new studies have started. Three have so far commenced in 2003: invasive fungal infection in very low birth weight infants (February); severe hyperbilirubinaemia (May); Langerhans cell histiocytosis (June); and a fourth, neonatal herpes simplex virus infection, has been approved and will start later in the year.

We are anxious to encourage research among younger paediatricians. To this end, we have introduced a bursary scheme. Each year, around the time of the College spring meeting, we invite applications from paediatricians in training or consultants not working in an academic institution. The application needs to identify an area of research suitable for the BPSU methodology and the successful candidate will receive £15,000 to cover the SU expenses and some research support. Help is offered to work-up a promising project to the level of detail needed before final acceptance on the orange card.

On the subject of funding, the time has come for us to seek support for the BPSU activities. At present we are entering the last year of support from the Department of Health and have initiated a dialogue to, hopefully, secure support for another three years. This is clearly a high priority for the next few months.

Last year I wrote about some concerns related to the new laws that impact on issues of the confidentiality of patient identifiable data. This continues to be an important issue and we are in active discussion with the Patient Information Advisory Group which has the responsibility for administering the regulations. A related aim is to make the BPSU more accessible to the medical profession and the public. Our website (http://bpsu.inopsu.com) provides a valuable contact point presenting information on methodology, application procedures, recent or new studies and much more. In addition, we have spent some time producing explanatory leaflets for both paediatricians and the wider public.

To finish, I would like to thank all those that make the BPSU work: the members of the Executive Committee; the administrative staff; the RCPCH; the investigators who initiate and carry through the studies; but most of all the more than 2100 paediatricians who complete the cards every month.

Professor Mike Preece

Chairman of the BPSU Executive Committee

1 Introduction

Rare diseases and infections are, paradoxically, a numerically important cause of morbidity and mortality in childhood. Individually uncommon, together they number thousands, and many result in severe sequelae. Many are characterised by chronicity and by high rates of disabling sequelae or death. Most pose a large financial and emotional burden for affected children, their families and health systems.

To address this problem in the UK and the Republic of Ireland in July 1986 the British Paediatric Surveillance Unit (BPSU) was set up, enabling paediatricians to participate in the surveillance and further study of uncommon disorders affecting children.

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

Several agencies collaborate in the BPSU: the Royal College of Paediatrics and Child Health (RCPCH), the Health Protection Agency (formerly the Public Health Laboratory Service), the Centre for Epidemiology and Biostatistics at the Institute of Child Health, London (ICH), the Scottish Centre for Infection and Environmental Health (SCIEH) which administers the scheme in Scotland and the Faculty of Paediatrics of the Royal College of Physicians of Ireland. As the BPSU monitors conditions of public health importance, an observer from the Department of Health attends the BPSU's Executive Committee, which meets every eight weeks to consider individual applications and the progress of studies.

The aims of the Unit are summarised in the box below.

This report mainly focuses on activities undertaken during the year 2002. Reference is also made to studies and activities, which commenced in the year 2003.

Aims of the British Paediatric Surveillance Unit

To:

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

June 1995 - adapted from prior documentation

2 How the surveillance system works

Selection of studies for inclusion in the scheme

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

The number of conditions under surveillance is usually limited to 12 and there is keen competition for places on the BPSU card. The BPSU application procedure consists of two phases, details of which can now be downloaded from the website at http://bpsu.inopsu.com/methodl.htm or is available on request from the BPSU office.

Factors that increase the likelihood of a study being accepted include scientific importance, rarity of the condition, proposals with outcomes of clear importance to public health, clear achievable objectives. Once approved by the BPSU Executive, studies require Multi Research Ethics Committee (MREC) approval before commencement.

The reporting system

Those participating in the reporting system include consultant paediatricians who are either members of the RCPCH or the Faculty of Paediatrics of the Royal College of Physicians of Ireland.

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

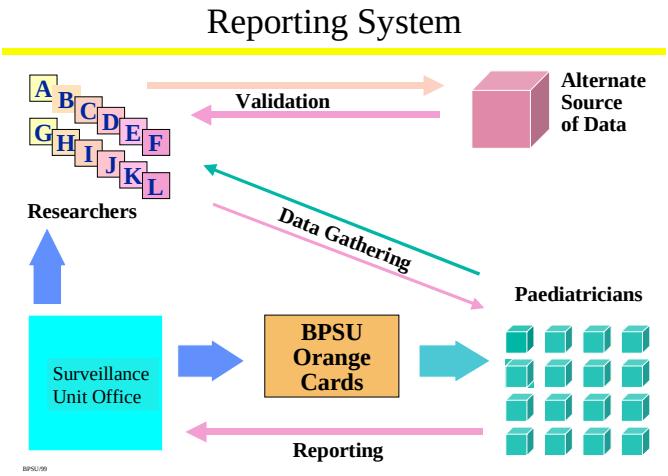
Respondents are asked to return the card to the BPSU office, indicating the number of cases of each condition on the card, which they have seen during the preceding calendar month. Scottish paediatricians return their completed cards via the Scottish Centre for Infection and Environmental Health. When reporting a positive case, respondents are also asked to complete the clinicians' tear-off section making a note of the case and **keeping** the details for future reference. This is required, as there have been occasions when clinicians have been contacted and they have been unable to recall the case.

Participants are expected to return cards even if they have no cases to report - there is a 'nothing to report' box on the card for them to tick. This is an important feature of the surveillance scheme as it allows non-responders to be identified; follow-up reminders are sent to all participants in the scheme who have not returned their card for two consecutive months. Overall compliance rates are continually monitored. During this whole process at **no** time does the BPSU office receive patient details.

Follow-up and confirmation of case reports

On receiving a case report the BPSU informs the relevant investigating team who contact the reporting clinician for further information about the case, in accordance with the agreed protocol for the particular study. Particular care is taken to ensure that questionnaires sent to reporting clinicians are as short as possible, clear, straightforward and not excessive in their demands. The amount of patient identifiable data collected is strictly limited, though not to an extent that would compromise study aims. The investigators subsequently report back to the BPSU on the outcome of each case follow-up, indicating when cases have been confirmed as meeting the case definition and identifying duplicate case reports - see Figure 1. Duplication of reporting is most likely to occur when the condition requires referral to a tertiary unit, but this is encouraged, as it is better to receive duplication than miss the chance of receiving a report.

Figure 1



The extent to which investigators receive survey data, identifying incorrect reports and duplicates and the speed in which this is done is known as the **'completion rate'**. Table 2 (page 8) shows the number of cases reported to the BPSU from its inception until the end of year 2002 for all the conditions under surveillance during year 2003. The number of cases which have so far been subsequently confirmed as meeting the case definition are also shown.

The time taken to follow-up a case report varies greatly between conditions and may be longer if microbiological or pathological details are required to confirm a case. The completion rate is high. For example, of the conditions under surveillance at the end of year 2002, only 286 (5%) of the 5712 case reports had yet to be followed-up. As a study draws to a close this completion rate figure will rise. The final completion rate normally averages average between 90-98%. There may however be delays in reporting outcomes to the BPSU office when there is the need for the collection pathology specimens.

Table 3 (page 8) summarises the outcome of the follow-up of all cases reported to the BPSU by the end of year 2002 and provides evidence for the level of accuracy of reporting by participating clinicians.

Classification of case reports

Valid reports:

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

Invalid reports:

These include:

duplicate reports of cases already reported to the BPSU,

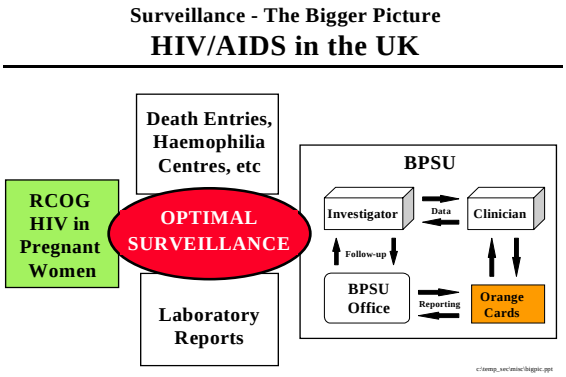
and

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

Outcome not yet known:

Outcome of follow-up not yet received by BPSU (by June 2003).

Figure 2



Where necessary to improve case ascertainment consultants working in a number of other specialties have been invited to participate in the scheme. For example since 1992, pathologists who are not members of the RCPCH have also been included in the reporting scheme. In addition, most studies of infections use laboratory reports to microbiologists e.g. HIV/AIDS and congenital rubella. Other current studies that are benefiting from such multiple ascertainment include cerebral vascular disease and thrombosis studies who are also ascertaining cases through members of the British Society of Haematologists. Apart from helping to improve ascertainment such complimentary data sources help to validate the surveillance system (Figure 2).

Funding

For the three-year period to September 2004 the BPSU is in receipt of a grant from the Department of Health (DH). This contribution supports a substantial percentage of the Unit's running costs. In addition, the BPSU asks surveillance teams to contribute a sum to cover the printing/distribution of the orange cards, and where possible the administrative costs of coordinating the study. This sum is currently £7,600 for a 13-month study, though a lower rate of £3,900 exists for those who are applying for funds from small local sources. These funding sources manage to cover the day-to-day costs of running the Unit.

Further non-cost support is received from the Royal College of Paediatrics and Child Health, the Health Protection Agency (Communicable Disease Surveillance Unit), the Scottish Centre for Infection and Environmental Health and the Institute of Child Health (London).

The Unit was also in receipt of donations from the Wellcome Trust and Wyeth Vaccines, who contributed towards the costs of the second conference of the International Network Paediatric Surveillance Units, held in April 2002.

3 Surveillance activities in 2002

Three studies commenced in 2002: June saw the start of a 13-month study into suspected fatal adverse drug reactions in children. July saw the commencement of the second BPSU survey into congenital toxoplasmosis, the first being undertaken in 1990. The third study, severe complications to varicella (chickenpox), commenced in November and will run for 13 months.

The cerebrovascular disease/stroke and like illness was the only study to be completed in 2002, ending in March, though a one year follow-up was undertaken and has just been completed.

Seven studies in 2002 had their period of surveillance extended for a further year, HIV/AIDS, congenital rubella, progressive intellectual and neurological deterioration (PIND), vitamin K deficiency bleeding, internal abdominal injuries, thrombosis in childhood and congenital cytomegalovirus. The last four were completed this spring. By December 2002, forty-nine studies had been completed since the BPSU's inception in June 1986 - those completed prior to the year 2001 are listed in Appendix A. Investigators are encouraged to inform the Unit when data gained through the BPSU is published or presented. Known publications and presentations in 2002/2003 relating to these studies and the Unit's work totaled 49 and are listed in Appendices B and C.

Three studies have so far commenced in 2003, invasive fungal infection in very low birth weight infants (February), severe hyperbilirubinaemia in the newborn (May), Langerhans cell histiocytosis (June), and a fourth, neonatal herpes simplex virus infection, has been approved.

The BPSU continues to disseminate information on its activities to clinicians and the public alike. This is achieved mainly through this report, the quarterly bulletin and increasingly through the BPSU website. This site (http://bpsu.inopsu.com) was re-launched in October 2001 and now contains the definitive papers for completed BPSU studies. The site is also accessible through the new RCPCH website at <www.rcpch.ac.uk/research/bpsu.htm>.

Through its position as "server" the BPSU continues to contribute to the work of the International Network of Paediatric Surveillance Units (INoPSU). Following a similar meeting in Ottawa two years ago, in April 2002 the BPSU hosted a second successful INoPSU conference. This was held over two days at York University, in conjunction with the Annual Scientific meeting of the College. The meeting was described in detail in last years report. The first INoPSU report has now been completed and can be viewed on the BPSU website and the recently re-vamped INoPSU website (www.inopsu.com).

Participation in the scheme during the year 2002

The BPSU ascertains the names of new consultants primarily through the RCPCH advisory appointment committees, membership office, BMJ adverts, through personal communication and with the ongoing College manpower census. During the year, 213 consultants were placed on the mailing list whilst 94 were removed, ostensibly following retirement. The number of consultant paediatricians participating in the scheme during the year 2002 therefore rose to 2299, an increase of 4.3% on the previous year. It should, however, be noted that some paediatricians who hold consultant status are excluded, as they do not undertake relevant clinical work, or else colleagues report on their behalf. The BPSU mailing list also includes selected groups of consultants other than paediatricians i.e. cardiologists, clinical geneticists and pathologists. In order to help in the ascertainment of cases pathologists continue to be included in the surveillance system, and our thanks are extended to the Royal College of Pathologists for supporting this initiative.

Reporting rates for returning the orange cards remains high - the overall card return compliance rate for the year 2002, calculated as a proportion of orange cards returned, was 92.3% (24097/26112), slightly down on 2001 (92.7%). Monthly response rates ranged from 94% in January to 90.1% in December, with a median of 92.2%**.** The overall response rate remains above 90% though a slight fall of on the year has been seen. To maintain this compliance rate respondents who have not returned cards for two consecutive months are sent letters, as much to verify postal address as to act as a reminder. Of those responders not returning cards less than 1% are considered as persistent non-responders. The return rate however is considerably higher than any equivalent UK scheme and ranks sixth of the 14 other national paediatric units (Table 13, page 41).

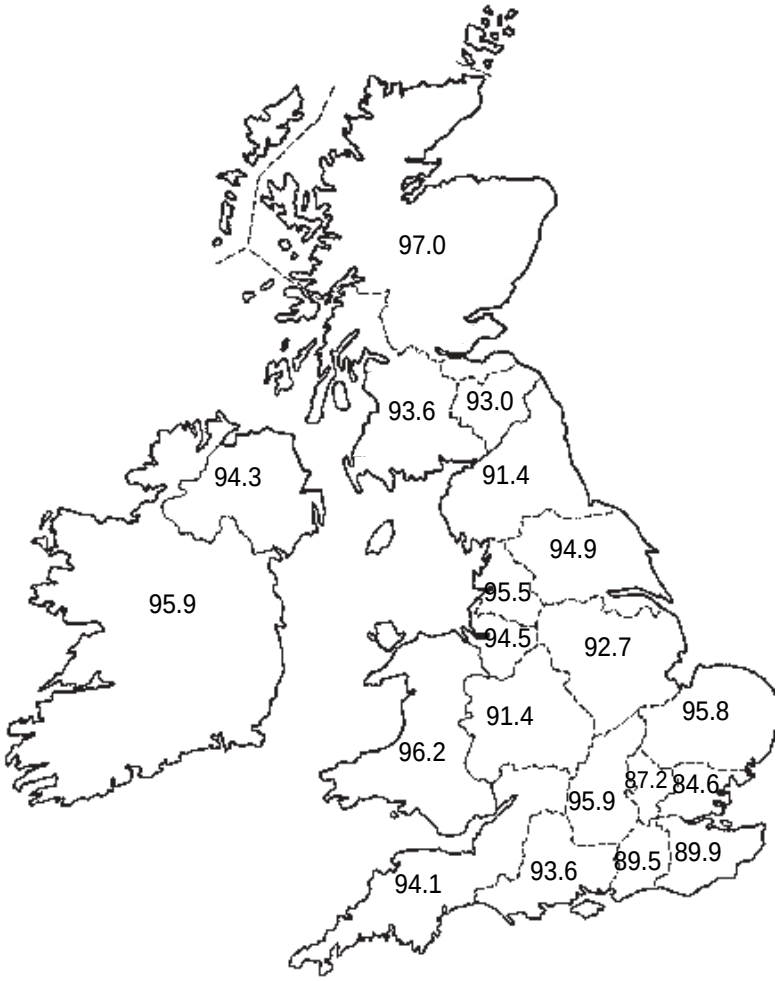
As in previous years, reporting rates varied considerably across the country, as is shown in Figure 3. North Scotland once again achieved the highest average yearly response rate – 97%%, with Wales again a close second (96.2%). The Thames area showed a cumulative response rate of 87.5% with North East Thames returning just 84.6% of cards. With so many teaching hospitals in London there is concern that cases may be going unreported. However, it should be recognised that there are many paediatric specialists in London who receive the orange card but are never

likely to see the conditions and thus may be less likely to return the cards on a regular basis, though we would encourage them to do so. With regard to rank order over the year, the Republic of Ireland rose 16 places to joint third and East Anglia and Yorkshire rose 11 places to fifth and seventh respectively. North West Thames fell 12 places to 19th and West Midlands fell 10 places to rank 15th. (Table 1). Overall, the response to the system can still be considered as excellent.

Table 1 *Regional ranking 2001 and 2002*

Region	Rank 2002	Rank 2001
Northern	15	8
Yorkshire	7	18
Trent	14	17
E Anglia	5	14
NWT	19	7
NET	20	20
SET	17	16
SWT	18	11
Wessex	11	4
Oxford	3	3
SWest	10	15
WMids	15	5
Mersey	8	6
NWest	6	9
Welsh	2	2
NScot	1	1
SScot	13	13
WScot	11	12
NIre	9	4
RIre	3	19

Figure 3 *Average orange card return rate (%) by area, 2002*



Workload of those reporting in the scheme

The BPSU continually monitors the workload of participants in the scheme in terms of the number of cases reported. 74 percent (1692) of participants reported no cases in 2002, more than in 2001 (67%). Twenty-five per cent (574) reported between one and four cases and only 1.4% (33) reported five or more cases. The greatest number of cases reported by a single paediatrician was 91. Specialties that had a particularly high level of reporting were, paediatric neurologists (PIND) and neonatologists (AIDS/ HIV, congenital cytomegalovirus) who with the commencement of the invasive fungal infections in VLBW infants and the hyperbilirubuinaemia in the newborn will once again carry a heavy burden in the forthcoming year. Community paediatricians continue to make a significant contribution to the reporting and their continued involvement in the scheme is very much required. With the continuation of the PIND and HIV studies this important contribution to continue in 2003.

Table 2 *Cases reported from June 1986 - December 2002 of conditions under surveillance in the year 2003.*

		Reports (confirmed cases)			
Conditions under Surveillance	Date when reporting began	**June 1986-Dec-95**	**Jan 1996-Dec-00**	**2001**	**2002**
HIV/AIDS	Jun-86	991 (691)	1017(693)	447 (319)	595 (437)
Congenital rubella	Jun-91	72 (39)	49 (25)	12 (1)	7 (1)
PIND	May-97	__ __	1066 (646)	200 (137)	225 (114)
CVD/S	Jan-01	__ __	__ __	299(204)	14 (10)
Vitamin K deficiency Bleeding	Jan-01	__ __	__ __	26 (4)	16 (3)
Congenital cytomegalovirus	Feb-01	__ __	__ __	135 (75)	134 (83)
Thrombosis	Feb-01	__ __	__ __	124 (67)	161 (89)
Internal abdominal injury	Mar-01	__ __	__ __	47 (14)	22 (8)
SFARec	Jun-02	__ __	__ __	__ __	8 (4)
Congenital Toxoplasmosis	Jul-02	__ __	__ __	__ __	16 (0)
Severe complications of varicella	Nov-02	__ __	__ __	__ __	29 (15)
Total		**1063 (730)**	**2132 ((1364)**	**1290 (821)**	**1227 (761)**

HIV/AIDS	Acquired immune deficeiency syndrome/human immunodeficiency virus: reports of AIDS in June 1986 includes cases previously seen; case definition extended to include HIV infection in January 1990.
PIND	Progressive Intellectual and Neurological Deterioration
CVD/S	Cerebrovascular disease, stroke and like illness includes Sturge-Weber and Vein of Galen
SFARec	Suspected Fatal Adverse Drug Reaction

Table 3 *Outcome of follow-up of the cases reported in 2002 of conditions under surveillance during the year 2003*

	Valid reports	**(%)**	**Invalid reports**			**Not yet**		
Condition under surveillance			**Duplicate**	**Errors**	**Total(%)**	**known**	**(%)**	**Total**
HIV/AIDS	2,140	(70)	351	472	(27)	87	3	3050
Congeital rubella	66	(47)	24	46	(50)	4	3	140
PIND	897	(60)	162	369	(36)	63	4	1491
CVD/S	214	(68)	13	56	(22)	30	10	313
Vitamin K deficency bleeding	7	(17)	4	14	(43)	17	40	42
Thrombsis	156	(55)	30	68	(34)	31	11	285
Congenital cytomegalovirus*	158	(59)	36	42	(29)	33	12	269
Internal abdominal injury	22	(32)	18	23	(59)	6	9	69
SFARec	4	(50)	0	3	(38)	1	13	8
Congenital Toxoplasmosis*	0	(0)	1	13	(88)	2	13	16
Severe complications of varicella	15	(52)	1	1	(7)	12	41	29
All	3679	(64)	640	1107	(31)	286	5	5712

*Validation depends on microbiological/pathological details

4 Main findings of studies undertaken in 2002

A 13-month surveillance of **cerebrovascular disease/stroke & like illness** (page 10) was completed in March 2002. Preliminary data are presented whilst data collection is completed. To date 315 notifications have been received of which 242 cases have so far been confirmed. This includes five cases of vein of Galen and two of Sturge-Weber. Seven deaths have already been identified and this is concerning.

After 25 months of **congenital cytomegalovirus** (page 12) surveillance, 93 confirmed and 69 possible cases have been reported through the BPSU, with a further 22 reports still being investigated. 25 additional cases have been reported through the laboratories. 20% of cases were identified antenatally. Over 40% of the confirmed cases had neurological signs (microcephaly, seizures, intracranial calcification), and sadly to date there have been seven deaths.

Surveillance for **congenital rubella** (page 14) has been underway in the UK continuously since 1971. Eight infants born since 1999 have been reported; in five of these cases the maternal infection was acquired abroad. The current level of MMR uptake gives cause for concern, as it may not be enough to prevent circulation of rubella infection in the long term.

Surveillance of **congenital toxoplasmosis** commenced in July 2003 for a period of thirteen months initially. To April 2004 forty-eight suspected cases had been made (21 through the BPSU and 23 through the BOSU, and four through laboratories). Of these nine cases (one definite, one probable and seven possible) were diagnosed during the study period.

The BPSU survey of **HIV and AIDS** (page 19) is the prime source of paediatric data on this condition in the UK and RoI. Almost all new infections are acquired through mother to child transmission and although most reports continue to come from the London area, cases are being notified from all parts of the country. The prevalence of HIV infection in pregnant women in the UK and RoI has increased substantially in recent years while the routine offer and recommendation of antenatal HIV testing has led to rising antenatal detection rates. It is not surprising therefore that reports of infants born to HIV infected women have also increased substantially while the proportion of infants who are themselves infected is declining

Surveillance of **internal abdominal injury due to child abuse** (page 21) commenced in March 2001 and ended in March 2003. 26 cases have been confirmed. Sadly in seven of the nine cases the child died from their internal abdominal injury. Preliminary findings also suggest that small bowel/duodenal injury is more common in non-accidental injury than accidental injury due to road traffic accidents and falls.

Despite the complexity of the conditions involved the survey of **progressive intellectual and neurological deterioration in children** (PIND) (page 23) has proved successful. It is being undertaken to identify any cases of variant Creutzfeldt-Jakob disease (vCJD) in UK children. Over 1500 cases of suspected PIND have been reported. Among them 625 cases are confirmed diagnoses, consisting of 104 different conditions. Six cases of vCJD have been identified.

A 13-month surveillance of **severe complications of varicella (chickenpox)** commenced in November 2002. Its primary objective is to estimate the annual incidence of complicated varicella in hospitalised children less than 16 years of age. To date 89 cases have been notified in the first five months and these are currently being followed up.

The 13-month survey into **suspected fatal adverse drug reactions** commenced in July 2002. To date eight reports have been notified through the BPSU orange card, four of which have been confirmed. A further 10 reports were received through the medical control agency 'yellow card' system. The number of cases is less than expected, this may reflect the true rate or point to possible underreporting.

The study into **thrombosis in childhood** (page 30) ended in March 2003 after 25 months surveillance. During this period 172 confirmed cases have been received. The main risk factors were central venous/femoral lines, infection and malignancy. Of these 129 (75/%) achieved partial or complete resolution. Overall mortality was low (7%) with no death attributed to venous thromboembolism.

The third BPSU survey of **vitamin K deficiency bleeding** (page 31) ended in February 2003. To date, of the 39 reports, seven fit the case definition. Four of the cases presented in the first week of life, one at 39 days and the other two at eight weeks. Four had received no vitamin K; two had oral prophylaxis and one intramusular vitamin K 0.5 mg. In four cases vitamin K prophylaxis was not given because parental consent was withheld

5 Surveillance studies undertaken in 2002

During the year 2002, 11 conditions were the subject of surveillance. One study, cerebrovascular disease/stroke like illness ended. Three studies commenced; suspected fatal adverse drug reactions in childhood (June), congenital toxoplasmosis (July), and in November, severe complication to varicella (chickenpox).

Three studies have so far commenced in 2003: invasive fungal infections in very low birth weight infants, severe hyperbilirubinaemia in the newborn and Langerhans cell histiocytosis with a fourth, neonatal herpes simplex virus infection due to start in the autumn of 2003. These are described in Chapter 6. On behalf of all the investigators the BPSU would like to thank all those who reported cases and contributed data that has led to the reports described below.

Table 4 *Studies underway in the year 2002*

Page	Study	Principal Investigators	Research Institution
10	Cerebrovascular disease/stoke & like illness	F Kirkham, A N Williams, S Aylett, V Ganesan,	Southampton University Hospital, Birmingham Children's Hospital, GOS
12	Congenital rubella*	P Tookey, C Peckham	ICH (London)
14	Congenital cytomegalovirus	P Tookey	ICH (London)
16	Congenital toxoplasmosis*	R Gilbert, M Stanford, S Cliffe	ICH (London), Kings College Hospital
19	HIV/AIDS in childhood*	P Tookey, A Nicoll, D Goldberg	ICH (London), PHLS, SCIEH
21	Internal abdominal injury due to child abuse	Professor J Sibert	University of Wales
23	Progressive intellectual and neurological deterioration*	C Verity, G Devereux, L Stellatano, A Nicoll, R Will	Addenbrookes Hospital, PHLS, CJDSU
27	Severe complications of varicella*	C Bramley	SCIEH
28	Suspected fatal adverse drug reactions	K Cheng, T Stephenson	Medical Control Agency, QMC Nottingham
29	Thrombosis in childhood	B Gibson, D Henderson	RHSC Glasgow
31	Vitamin K deficiency bleeding	J Tripp, A McNinch	Royal Devon & Exeter Hospital

*Studies still in progress as of July 2003

Cerebrovascular disease/stroke and like illness

Key Points

- **315 notifications have been received, of which 239 have so far been confirmed with a further seven Vein of Galen and two Sturge-Weber syndrome cases.**
- **Incidence was 1.94 per 100,000.**
- **There have been 22 deaths.**

Background

Cerebrovascular disorders in childhood are associated with significant mortality and considerable residual handicap, both physical and cognitive. For the United Kingdom, however, the actual numbers of children affected annually by stroke remains unknown. This 13 month study is a prospective observational study of one year's cases with independent surveying of British neurosurgeons, cardiac surgeons, cardiologists, paediatric radiologists and haematologists/oncologists.

The aetiology of stroke and cerebrovascular disease in childhood remains a puzzle in a significant proportion of cases. Even where there appears to be an association, causation may remain unproven. Management strategies have been developed for certain conditions, but there is no overall policy yet. The most important questions that doctors face is how far to investigate children with cerebrovascular disease or stroke, whether to refer and whether to treat. This surveillance study will also look at current practice.

Objectives

- To estimate the incidence of stroke, stroke-like illness and cerebrovascular disease in all children between birth (at >37 weeks gestation) and 16 years.
- To determine the national and regional patterns of presentation and of neurological referral.
- To assess aetiology considered at the time of diagnosis in incident cases, and to describe current practices regarding management, investigation and prevention of recurrence.

Surveillance Period

January 2001- January 2002 (inclusive).

Case definition

Any child from birth (at >37 weeks gestation) to the 16th birthday with cerebrovascular disease and/or stroke or stroke-like illness. The World Health Organisation (WHO). definition of stroke is: "A clinical syndrome of rapidly developed clinical signs of focal or global disturbance of cerebral function lasting greater than 24 hours or leading to death with no obvious cause other than that of vascular origin."

To Include: children with cerebrovascular disease presenting in other ways e.g.

- haemorrhage or infarct in a vascular territory with disturbance of cerebral function for less than two hours
- moyamoya
- venous sinus thrombosis
- Sturge-Weber syndrome presenting as epilepsy
- Vein of Galen malformation presenting as cardiac failure
- 'stroke-like episodes' lasting more than 24 hours without an obvious vascular cause e.g. in migraine or metabolic disease
- focal intracerebral haemorrhage or ischaemic infarct related to severe head injury.

This does not automatically exclude prior illness e.g. infection or events e.g. head trauma, provided that this is linked to the clinical presentation via a vascular mechanism.

To Exclude:

- non-cerebral venous and arterial thrombosis
- subdural/extradural haematoma
- neonatal intraventricular haemorrhage and periventricular leukomalacia
- hemiparesis after seizures (Todd's paresis) unless cerebrovascular disease.

Analysis

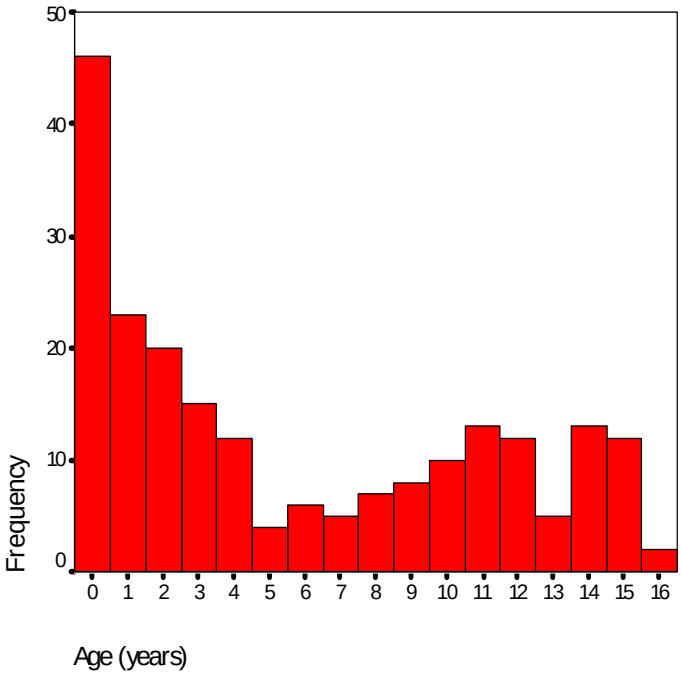
The Childhood Stroke study[1] ran from Jan 1st 2001 – 31st Jan 2002. Four hundred and ten cases reports were received, 315 (77%) notifications via the BPSU, and 105 (23%) through the additional surveys of neurosurgeons, radiologists, paediatric cardiologists, cardiothoracic surgeons and haematologists.

Of these 297 have so far been confirmed as meeting the case definition. After removal of duplicates, patients with vein of Galen (n=7) and those with Sturge-Weber syndrome (n=2), analysis of the data on the remaining 239 patients has commenced.

The estimated incidence of 1.94 cases per 100,000 per annum in the UK is a little lower than the incidence obtained from the only previous study in the UK, the Oxfordshire Community Stroke project[2], which suggested an incidence of 3/100,000 based on a very small number of cases.

139 (58%) of patients were male. Median age at stroke was four years (range birth to 15.99 years). Thirty-one (13%) strokes occurred within the first month of life. Stroke appeared to be less common in mid-childhood than in the pre-school and early teenage years (Figure 4).

Figure 4 *Histogram to show the age distribution of cases with stroke during childhood*



On neuroimaging, 136 (54%) children had focal ischaemia, 62 (26%) had haemorrhage and the remainder had either normal parenchymal imaging or another abnormality.

Of the 204 for whom data are available at this stage, 24 (12%) had congenital heart disease, 26 (13%) had a haematological disorder (nine abnormal on sickle screening), 11 (5%) had renal disease, nine (4%) were immunodeficient and three (1%) had an autoimmune condition.

From data available from the initial questionnaire, 22 children (9%) died. Recurrence and outcome are being examined through six-month and one year follow-ups. Mortality data from the National Office of Statistics will be available later in the year along with the six and 12 month follow-ups.

In summary, although vein of Galen malformations and Sturge-Weber syndrome are rare, stroke affects approximately two children per 100,000 in the United Kingdom every year. Neonates and young children appear to be particularly at risk and there is a significant mortality in this population. From these data, ischaemic stroke appears to be twice as common as haemorrhage. At least one third of the children have a pre-existing condition and this might be a group in whom interventions might be targeted at prevention.

Funding

The Stroke Association, Stroke House, 240 City Road, London EC1V 2PR. Tel: 020 7566 0348, Fax: 020 7490 2686
Web: http://www.stroke.org.uk

Support Groups

1. Stroke Association, Stroke House, 240 City Road, London EC1V 2PR. Tel: 020 7566 0348, Fax: 020 7490 2686
   Web: http://www.stroke.org.uk
2. Different Strokes, 9 Canon Harnett Court, Wolverton Mill, Milton Keynes, MK12 5NF. Tel: 0845 130 7172 Fax: 01908 313501 Web: http://www.differentstrokes.co.uk
3. Sturge-Weber Foundation (UK), Burleigh, 348 Pinhoe Road, Exeter EX4 8AF Tel: 01392 464675 Fax: 01392 464675
   Web: http://www.sturgeweber.org.uk
4. Vein of Galen Parents Support Group, 28 Southgate Drive, Wincanton, Somerset, BA9 9ET
   Web: http://www.veinofgalen.co.uk
5. Sickle Cell Society, 54 Station Road, London, NW10 4UA
   Tel: 020 8961 7795 Fax: 020 8961 8346
   Web: http://www.sicklecellsociety.org

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Congenital cytomegalovirus (cCMV)

Key points

- **Infants with congenital CMV who are asymptomatic at birth are unlikely to be diagnosed.**
- **Perinatal and postnatal acquisition of infection is common, and confirmation of congenital infection relies on clinical samples taken in the first three weeks of life.**
- **20% of reported infants with congenital CMV were diagnosed because maternal or fetal infection was suspected antenatally, and another 50% presented with neurological symptoms at birth.**
- **About 15% of infants with confirmed cCMV received ganciclovir, including about 40% of those who presented with neurological signs. A high proportion of infants reported with confirmed or suspected cCMV were born before 37 weeks gestation. This probably reflects both the fact that infants with symptomatic congenital CMV are more likely to be born early, and that premature infants are likely to have investigations which may coincidentally reveal cCMV.**

Background

Congenital CMV (cCMV) was put on the orange card in February 2001, and remained there for 25 months. Infants born in 2001 or 2002 and diagnosed with confirmed or suspected cCMV should have been reported. Infants with cCMV who were asymptomatic at birth or had non-specific symptoms are unlikely to have been identified.

Primary or recurrent maternal CMV infection in pregnancy can result in fetal infection. Although most infants have no associated problems, cCMV can cause neonatal death or severe disease, and long-term disability in 10-20% of infected children. Incidence of cCMV ranges from 0.3% to 2% of all live births worldwide; earlier British studies suggest an incidence of 3-4/1000 live births, but this varies in different population groups, and may have changed over time. Congenital infection can only be confirmed on the basis of samples collected in the first three weeks of life, and detection of CMV in later samples is likely to reflect infection acquired at delivery or postnatally, which is common, but rarely associated with adverse outcome.

In Britain about 20% of children become infected by 12 months of age[1] About 10% of congenitally infected infants are symptomatic at birth, and most of these have long-term complications, for example cerebral palsy, mental retardation and sensorineural hearing loss (SNHL). In contrast, most asymptomatic infants develop normally, although a minority have neurological sequelae, usually SNHL.

Objectives

The study was established to ascertain the population prevalence of clinically recognised congenital CMV infection in infants born in the British Isles, current management strategies, and the clinical disease outcome, and to explore the feasibility of using routinely collected neonatal dried blood spots to confirm or exclude a diagnosis of congenital CMV infection in infants who present after three weeks of age.

Surveillance period

February 2001 - February 2003 (inclusive).

Case definition

Any infant with confirmed or suspected cCMV infection born in the UK or Republic of Ireland since 1 January 2001.

Confirmed cases: any infant with cCMV infection, confirmed by PCR or virus isolation from urine, blood, saliva or tissue taken at biopsy within three weeks of birth.

Suspected cases: any infant with symptoms compatible with cCMV infection aged under 12 months with CMV isolated from urine, blood, saliva or tissue taken at biopsy after three weeks of age, and/or with CMV specific IgM after three weeks of age.

Analysis

During the 25 month period February 2001 to February 2003, 288 BPSU reports were received (Table 5), which included 93 confirmed and 69 suspected cases (diagnosis after three weeks of age); 19 of these confirmed and suspected cases were reported through the laboratory reporting system first. There were 93 duplicates or error reports; among these were 24 infants born prior to 2001, and six (to date) born in 2003. Eleven reports made in 2001 are outstanding and are unlikely to be classified, and another 22 reports made more recently are still being followed up. Country of report is also shown in the table.

Another 25 infants diagnosed in the first three weeks of life have been reported through the laboratory reporting system without a corresponding paediatric report to date, and there are therefore few details about these cases as yet.

Preliminary observations

Among the 93 infants with confirmed cCMV for whom information is available, there were five twin pairs where both infants were infected, and another two infants who each had an uninfected twin. The twins were delivered at between 28 and 35 weeks. The mean gestation of the 81 singleton infants was 36 weeks, and mean birthweight was 2330gms. In about 20% of pregnancies maternal CMV infection in pregnancy had been diagnosed antenatally, usually following the investigation of flu-like illness in the mother, or abnormal fetal ultrasound findings. At least 40% of the confirmed cases had neurological signs (microcephaly, seizures, intracranial calcification), and over a third of those were treated with gancyclovir. Those without neurological signs were generally diagnosed following an antenatal diagnosis, or investigation of non-specific symptoms in the neonatal period. Seven infants are known to have died, one at birth, four in the first month, one at six weeks and one at eight months. Outcome in the second year of life is being sought for the survivors through the notifying paediatrician.

Among the 69 infants reported with possible cCMV, almost half were born before 37 weeks gestation (and seven of these have died). Most of the other infants presented with problems after the neonatal period. A substantial proportion are likely to have acquired perinatal or postnatal infection, and we intend to try to clarify the timing of infection by testing dried blood spots collected at birth.

We wish to thank everyone who has notified cases and completed forms. If we have not already done so, we will be approaching you for summary outcome information during the second year of the child's life.

Funding

This study is funded from departmental resources.

Support Group

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Table 5 *Reports made through the BPSU to February 2002*

	Confirmed	Suspected	Duplicate or error	Outstanding	Total
England	77	61	70	24	232
Wales	2	2	5	2	11
Scotland	8	4	11	2	25
NI	1	1	2	2	6
RoI	5	1	5	3	14
Total	**93**	**69**	**93**	**33**	**288**

Reference

1. Peckham CS, Johnson C, Ades A, Pearl K, Chin KS. Early acquisition of cytomegalovirus infection. *Arch Dis Child* 1987; **62**:780-85

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Congenital rubella

Key Points

- **Since 1997 only eight congenital rubella births have been reported in the UK.**
- **In five of those cases, the infant's mother acquired infection outside the UK.**
- **The current level of MMR uptake may not be high enough to prevent renewed circulation of rubella infection and continued reporting of congenital rubella is required to monitor the situation.**
- **Women who have come to the UK as adults are likely to have higher rates of susceptibility than women who were born and brought up in the UK. They will be at higher risk of acquiring infection in pregnancy if rubella outbreaks occur.**

Background

Surveillance of congenital rubella in Scotland, Wales and England started in 1971 with passive reporting by audiologists, paediatricians and microbiologists. Following the introduction of vaccination for schoolgirls (1970) and susceptible women post-partum (1972) the number of reported congenital rubella births and rubella associated terminations declined from an average 50 births and 740 terminations a year in 1971-75 to an average 22 births and 54 terminations a year in 1986-90. Since there were so few cases, active surveillance was required, and congenital rubella first appeared on the orange card in January 1990. Since then, BPSU reports from Northern Ireland (NI) and the Republic of Ireland (RoI) have also been followed up, but are not normally included in published figures.

Since 1988 the combined Measles Mumps and Rubella vaccine (MMR) has been offered to all children in the second year of life, and in 1996 a second dose of MMR was introduced for four year olds, and the schoolgirl rubella vaccination programme was discontinued. The circulation of wild rubella virus has been at extremely low levels in the UK in recent years, and an increasing proportion of individuals are protected by vaccine-induced immunity. However, adverse publicity about unproven associations between MMR, bowel disease and autism have led to a decline in MMR uptake since the mid 1990s, and in the last quarter of 2002 the recorded uptake for two year olds was only 81%[1]. This is not sufficient for the long-term maintenance of herd immunity levels of 85-88%, which are required to prevent circulation of rubella infection, particularly since few children now acquire natural infection. It is possible that rubella could once again start to circulate in the UK, as it does in many other parts of the world. Awareness of rubella infection and congenital rubella among paediatricians, and health professionals looking after pregnant women must be maintained, and continued surveillance of congenital rubella is vital.

Objectives

To monitor the effectiveness of the rubella immunisation programme by determining the incidence of congenital rubella in England, Scotland and Wales and investigating the circumstances surrounding any new cases.

Surveillance period

Surveillance began in January 1990 and is reviewed annually.

Case definition

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

Analysis

BPSU notifications

There were seven notifications of congenital rubella to the BPSU in 2002, but none of them were newly confirmed cases born recently in the UK or RoI. Two were adolescents, one of whom had previously been reported, two were infants with congenital rubella who had been born abroad, and three were error reports.

Altogether since the beginning of active surveillance in 1990, 136 reports have been made through the BPSU (Table 6). Of the 121 reports from England, Scotland and Wales, 46 are confirmed or compatible, previously unreported cases of congenital rubella, four are possible cases, and 11 had already been reported from another source. The remaining reports were duplicates (19),

reporting errors (36) and five where further information could not be obtained. Fifteen reports were from the Republic of Ireland or Northern Ireland, and included three children with confirmed congenital rubella (one born in 1989 and two in 1996), and a fourth possible case (born in 1983). One report from the RoI is currently outstanding.

Congenital rubella 1990-2002

Fifty-three children with confirmed or compatible congenital rubella have been born and reported since the beginning of active surveillance in 1990 and over 70% were first reported through the BPSU (Table 7). Overall, about a quarter of the 53 children born since 1990 had mothers whose infection was acquired abroad. Another third were born to women who, although they acquired infection in the UK, had only arrived in the country relatively recently[2]. Three women had confirmed re-infection in pregnancy. There have also been 75 terminations for rubella disease or contact in pregnancy recorded by ONS in England and Wales during the period 1990-2001[3].

Recent reports

Eight infants with congenital rubella were born between 1999 and 2001 (Table 7). Although five cases resulted from maternal infection acquired abroad (Bangladesh, Pakistan, Sri Lanka, Nigeria and Zambia), three infants were born to women whose infection occurred in the UK [4,5]. One British-born woman acquired rubella in Scotland, although the infection was epidemiologically linked to an outbreak in Greece in 1999[6]. The remaining two maternal infections were acquired in London, one by a British-born woman, and the other by a Sri Lankan woman who had been in the UK for several years.

Results from antenatal rubella testing 1996-1999 in the (former) North West Thames region show that rubella susceptibility in pregnant women continues to vary by ethnic group, with women from many parts of Asia and Africa have particularly high susceptibility especially if they are having their first baby [7]. Women who have come to the UK from countries with less successful, or disrupted vaccination programmes are likely to be at higher risk if there is renewed circulation of rubella here. Even while rubella infection is rare in the UK, susceptible women who travel abroad during early pregnancy may come into contact with infection.

Table 7 Confirmed and compatible congenital rubella births reported to the NCRSP 1971-2002* (England, Scotland & Wales only)

Year of birth	Primary source of notification: BPSU	Other	Total
1964-69	0	39	39
1970-79	1	453	454
1980-89	13	320	333
1990-2002 ~	39	14	53*
1990	8	4	12
1991	2	1	3
1992**	5	2	7
1993	2	1	3
1994	5	2	7
1995	1	0	1
1996	9	3	12
1997	0	0	0
1998	0	0	0
1999	0	1	1
2000	4	0	4
2001	3	0	3
2002	0	0	0
Total	53	826	879

* The data for recent years are provisional
~ The data for 1990-2002 include 2 reported stillbirths
** Includes a set of triplets

It is essential that case ascertainment is as rapid and complete as possible, both for imported cases and those where infection was acquired in the UK. Please notify to the BPSU all infants with suspected congenital rubella, whether or not they have the associated typical defects. We are extremely grateful to all participating paediatricians, especially those who have notified cases and completed questionnaires.

Funding

The Health Protection Agency makes a contribution towards the costs of the surveillance.

Table 6 *Congenital rubella reports to BPSU 1990-2002 (includes births occurring in earlier years)*

	Registered cases	Already reported	Outstanding	Duplicate, error or lost	Total
England, Scotland and Wales	50	11	0	60	121
NI and RoI	4	2	1	8	15

Support Group

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Congenital toxoplasmosis

Key points:

- **Children with neurological manifestations of toxoplasmosis almost certainly acquired infection in utero, with the exception of children with immune deficiency disease.**
- **Toxoplasma infection most commonly presents with ocular symptoms. When symptoms present in infancy, infection is congenital. Thereafter, age at presentation with ocular disease, in the absence of previous symptoms or signs, is associated with an increased risk of postnatally acquired infection.**
- **To determine the birth prevalence of congenital toxoplasmosis, clinicians are being asked to report all toxoplasma infection in children. Clinical data and results from retrospective testing of stored Guthrie Card blood spots will be used to narrow the uncertainty about whether infection was congenital or postnatally acquired.**

Background

The study aims to determine the incidence of newly diagnosed, symptomatic toxoplasmosis in immune-competent children. Toxoplasmosis can be acquired in utero and postnatally[1]. The primary aim is to determine the birth prevalence of congenital toxoplasmosis, the form of infection seen most commonly by paediatricians. However, most children who develop symptoms due to toxoplasmosis (congenital or acquired) present to ophthalmologists with visual problems or symptoms of ocular inflammation. The study therefore involves paediatricians, ophthalmologists, and toxoplasma referral laboratories, in order to identify all children with symptomatic toxoplasma infection.

To determine whether toxoplasma infection is congenital or acquired, we will use clinical and serological data. Persistence of specific IgG beyond one year of age, or presence of specific IgM or IgA before 12 months virtually rules in congenital toxoplasmosisSerological testing will also be performed on stored Guthrie card blood spots. When positive, congenital infection is almost certain, but negative results are consistent with congenital or postnatal acquired infection [2]. Certain clinical findings, such as intracranial lesions, or signs of lymphadenopathy or hepatosplenomegaly in infancy, also make the diagnosis highly probable provided the child is IgG positive. Differentiation of the timing of infection is more difficult in children with retinochoroiditis alone, as lesions due to congenital and postnatally acquired infection are indistinguishable. However, the older the child at presentation, the greater the risk that infection was acquired after birth. Estimates of the incidence of congenital and postnatal infection, and the risk of symptomatic eye lesions will be used, to determine the probability of postnatal acquired or congenital infection[2].

Toxoplasmosis can be acquired by ingestion of infected undercooked meat or oocyst-contaminated soil or water. Preventive strategies include health information, and in some countries, prenatal or neonatal screening to identify and treat congenital toxoplasmosis[2,4,5]. The benefits of such policies depend

crucially on the burden of disease in terms of frequency and severity, and the effectiveness of treatment. The study will provide an estimate of the birth prevalence of symptomatic congenital toxoplasmosis, and of symptomatic toxoplasmosis in childhood acquired before or after birth.

Cases are ascertained through the BPSU scheme, the British Ophthalmologic Surveillance Unit (BOSU), and five referral toxoplasma laboratories in the British Isles. In addition, national data on terminations of pregnancy will be scrutinised for any mention of toxoplasmosis.

Objective

- To ascertain the birth prevalence, severity of clinical manifestations and age at first diagnosis.
- To determine the feasibility of using stored neonatal dried blood spots to confirm or exclude a diagnosis of CT infection in children.

Surveillance Period

July 2002- July 2004.

Case definition

Paediatricians are asked to report any child (<16 years) or stillbirth in whom congenital toxoplasmosis is suspected. This reporting definition includes any child with toxoplasma specific IgG antibodies or evidence of maternal infection and unexplained intracranial calcification, ventricular dilatation, microcephaly, retinochoroiditis, or microphthalmia, or unexplained lymphadenopathy or hepatosplenomegaly in infancy. Ophthalmologists are asked to report any child with unexplained retinitis.

Preliminary results and Discussion (August 2002 – April 2003)

By April 2003, 48 reports of suspected cases of congenital toxoplasmosis (CT) had been made (21 through BPSU, 23 through BOSU, and four through the laboratories) (Table 8). Further information is available for 29 of the 48 reports, 12 reports were errors and seven reports are currently outstanding. Two reports were duplicates (one received though BPSU and BOSU and one received through BPSU and Belfast Reference Laboratory)

Of the 27 non-duplicate reports of suspected CT, 21 were classified in the clinician's opinion as definitely, probably, or possibly congenital toxoplasmosis (Table 9 overleaf). Nine cases (one definite, one probable and seven possible) were diagnosed during the study period. In addition 12 cases (six definite, three probable and three possible) were reported where diagnosis was prior to the study period. In six reported cases, toxoplasma infection was considered unlikely (often miscarriages or stillbirths with serological evidence of maternal infection, but no test results to indicate fetal infection).

Further serological information on cases may be available from testing of stored Guthrie card blood spots for toxoplasma-specific IgM. Finally, we plan to continue surveillance for a further year in order to increase the number of cases in the study. An application to extend the study is underway.

Funding

The British Council for the Prevention of Blindness contributed to the funding of this project.

Table 8 *Reports of suspected CT by source of notification received by April 2003*

	No. of reports made	No. of questionnaires received	No. of outstanding questionnaires	No. of mis-reports
BPSU	21	12	3	6
BOSU	23	13	4	6
Ref. Labs				
St Georges'	0	-	-	-
Swansea	*	-	-	-
Inverness	**	-	-	-
Belfast	4	4	0	0
Dublin	**	-	-	-
Total	**48**	**29**	**7**	**12**

* Implementation of study currently underway ** No response from laboratory

Table 9

Reports of suspected CT by presence of retinochoroiditis lesions and congenital infection status

	Prospectively identified 1.7.02 – 1.4.03				**Retrospectively identified Before 1.7.02**			
	Congenital infection status				**Congenital infection status**			
	total	Definite	Probable	possible	total	Definite	Probable	possible
BPSU								
Toxoplasmosis in childhood								
Retinochoroiditis present	1	1**	-	-	7	5	1	1
Not present/NK	-	-	-	-	1	1	-	-
Total	**1**	**1**	**-**	**-**	**8**	**6**	**1**	**1**
BOSU								
Toxoplasmosis in childhood								
Retinochoroiditis present	8	-	1	7***	3	-	2	1***
Not present/NK	-	-	-	-	-	-	-	-
Total	**8**	**-**	**1**	**7**	**3**	**-**	**2**	**1**
Reference Labs*								
Total	**-**	**-**	**-**	**-**	**1**	**-**	**-**	**1**
Grand Total	**9**	**1**	**1**	**7**	**12**	**6**	**3**	**3**

* Further clinical data currently being collected

** This case was also reported through BOSU

*** These cases are considered to have toxoplasma retinochoroiditis which, based on the available data, is more likely to be due to postnatally acquired than congenital infection.

Acknowledgements

The investigators are very grateful to Paediatricians, Ophthalmologists and staff at the referral laboratories for taking the time to support this surveillance project.

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HIV/AIDS infection in childhood

Key points

- **Reports of infants born to HIV infected women have increased substantially in recent years.**
- **The proportion of infants born to HIV infected women who are themselves infected is declining.**
- **A significant number of older children, often recently arrived from endemic areas, continue to be reported.**
- **Annual follow up of infected and indeterminate children continues. Follow up of uninfected children to identify any possible adverse effects of exposure to prophylactic antiretroviral therapy is being established.**

Background

National surveillance of paediatric HIV infection and AIDS began in 1986 and is based on independent paediatric, obstetric and laboratory reporting schemes. All reporting is voluntary and confidential and data from all sources are combined as the National Study of HIV in Pregnancy and Childhood (NSHPC) at the Institute of Child Health[1].

Most children currently living with HIV in the UK and Republic of Ireland (RoI) acquired their infection through mother to child transmission. Antiretroviral treatment, delivery by elective caesarean section and the avoidance of breastfeeding, reduce transmission rates to around 1% in comparison with a likely transmission rate of about 25% without interventions. In order for women to access these interventions, the routine offer and recommendation of antenatal HIV testing to all pregnant women has been implemented in England[2] and the RoI. A similar policy is being implemented during 2003 in Scotland and Wales and piloted in Northern Ireland. Unlinked anonymous survey data[3] indicate that the annual number of infants born to HIV infected women (both diagnosed and un-diagnosed) has increased substantially in the UK from about 300 in 1997 to over 560 in 2001. However, the proportion of women diagnosed before delivery, who could benefit from interventions, increased from an estimated 32% to at least 77% over the same period[3] with a marked decline in the proportion of infected infants.

Objective

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

Surveillance Period

Surveillance began in June 1986 and is reviewed annually.

Case definition

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

Analysis

Number of reports: By the end of December 2002 there had been 2931 reports through the BPSU, of which 1911 were confirmed cases, 413 were duplicates and 439 were reporting errors. The remaining 168 reports were still being investigated. A further 1996 reports were from other notification sources; these include paediatric reports (mainly from three major London clinics) made directly to the NSHPC, laboratory reports to the Health Protection Agency CDSC and the Scottish Centre for Infection and Environmental Health, and obstetric reports made through a parallel obstetric reporting scheme run under the auspices of the Royal College of Obstetricians and Gynaecologists. Children who acquired HIV during the course of treatment for haemophilia were all born before 1984, and the majority were reported through the UK Haemophilia Centre. Table 10 shows the likely source of infection or exposure risk for all confirmed reports.

Table 10 *HIV infection and infants born to HIV infected women (all reporting sources)*

(notified by 31 December 2002)

Exposure / likely source of infection	BPSU reports	Reports from other sources	TOTAL
Born to HIV infected woman	1824	1727	3551*
Haemophilia treatment	48	219	267
Blood transfusion/products	31	18	49
Other/not yet established	8	32	40
Total	1911	1996	3907

Table 11 *Infection status of children born to HIV infected women (notified by 31/12/02)*

Region of first report	*Infected*	*Indeterminate*	*Not infected*	Total
England, Wales & N Ireland*	879	744	1264	2887
Scotland	44	37	180	261
Republic of Ireland	54	83	266	403
Total	977	864	1710	3551

* Over 80% reported from former Thames regions, <2% from Wales and NI combined

Summary data from the NSHPC are forwarded to the national surveillance centres on a quarterly basis, and contribute to the overall national surveillance of HIV infection. UK summary tables appear on a quarterly basis in the Communicable Disease Report (England, Wales and Northern Ireland) (available at www.phls.co.uk) and the SCIEH Weekly Report (Scotland).

Children born abroad: Eleven percent (440) of all 3907 children ever reported in the UK and RoI were born abroad and about 95% of these children are known to be infected. Nearly 50% (210) of children born abroad have been notified since 2000 and many were over five years old when first seen and came from areas where HIV infection is endemic. In some cases it was not possible to ascertain the route of transmission as the HIV status of the mother at the time of the child's birth is unknown.

Follow-up: Follow up information is sought for all infants born to infected women to establish their infection status. All infected children are followed up annually to monitor their clinical and immunological status. Enhanced follow up information for approximately 75% of infected children is currently collected through the Collaborative HIV Paediatric Study (CHIPS), a collaboration between the NSHPC, the MRC Clinical Trials Centre and the centres involved in PENTA treatment trials.

A growing number of children, most of whom are uninfected, have been exposed to antiretroviral therapy (ART) in fetal or early life. Maintaining contact with these children is important in order to monitor any unwanted side effects of treatment and we are now establishing on-going follow up of children exposed to ART (CHART study), with the help of reporting paediatricians and clinic staff.

Follow up of the surviving young adults infected in childhood during the course of treatment for haemophilia is undertaken by the UK Haemophilia Centre and the Health Protection Agency, CDSC HIV and STI Division.

Children born to infected women: Of the 3551 children born to HIV infected women and reported by the end of December 2002 (Table 11), 977 had confirmed infection and 1710 were known to be uninfected. Over a third of the infected children were born abroad. The 864 children whose infection status is currently classified as indeterminate include nearly 200 who were born before 2000, many of whom have either left the country or are otherwise lost to follow up.

The number of children born to HIV infected women in the UK and RoI has increased substantially in recent years (Figure 5). Over 95% of the approximately 650 indeterminate children born since 2000 were born to diagnosed women; most of these children are still in follow up and very few are likely to be infected.

Acknowledgments

We would like to thank all members of the RCPCH, particularly those paediatricians who have reported cases and completed questionnaires, for their continued support and diligence.

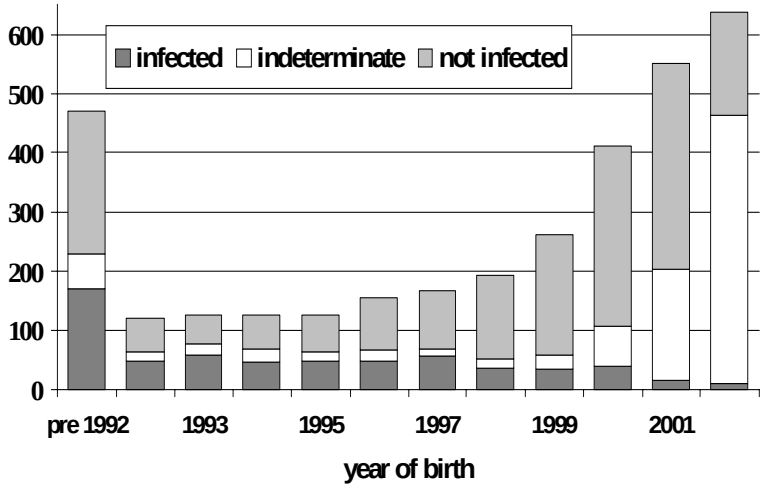

Figure 5 *Year of birth and infection status of children born in UK & Republic of Ireland to HIV infected women, and reported through BPSU and other sources by end March 2003*

Funding

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Support Groups

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

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Internal abdominal injury due to child abuse

Key points

- **Abdominal injury is a rare but serious form of abuse with a third of the children dying.**
- **Over half the children have small bowel injury.**
- **Two thirds of children have child protection concerns evident before the current episode of abuse.**

Background

Non-accidental injury in childhood is sadly a common occurrence in today's society. In the UK, according to a recent NSPCC survey[1], 7% of young adults have experienced serious physical injury at the hands of their carers during their childhood.

The skeletal and intra-cranial manifestations of physical child abuse are well described in the medical literature; with head injuries being the leading cause of death in children injured non-accidentally[2].

Internal abdominal injuries due to child abuse are also described but are thought to account for less than 2% of all non-accidental injuries[3]. However this type of injury is the second commonest cause of death following child abuse with mortality rates as high as 40-50% reported in the USA[4]. Child abuse has been identified along with motor vehicle trauma as the major aetiological factors in childhood internal abdominal injury[5].

There is only a small body of UK literature available on the subject of internal abdominal injury due to child abuse. Any of us involved in analysing a suspected case as part of a child protection investigation may be faced with real difficulties if we are looking for information. In the USA, it has been suggested that hollow viscous injury is the most commonly identified internal abdominal injury seen as a result of abuse whereas accidental injury is more likely to be associated with injury to solid organs within the abdomen, for example the spleen or kidney[5]. However, it is clear from available case reports that any internal abdominal organ can be injured following abuse.

There are a number of important questions to consider. For example, how common is this condition in the UK? How do children present and what is their eventual clinical outcome? What associated signs or injuries should be looked for in addition? Is there a pattern of injury that is more likely to indicate a non-accidental rather than an accidental cause? Are there any pointers to prevention?

This background prompted us to undertake a two-year study of internal abdominal injury due to child abuse, which is now nearing completion.

Surveillance Period

March 2001 to March 2003 (inclusive).

Objectives

- What is the incidence of internal abdominal injury due to child abuse?
- Which internal abdominal organs are involved?
- What are the key diagnostic features in differentiating between accidental injury and abusive injury?
- Were there factors prior to diagnosis that could have been acted upon and perhaps prevented the internal abdominal injury?
- What was the child protection outcome?

Case definition

Children aged 0-14 years, diagnosed as having an internal abdominal injury, attributed to child abuse following review of the circumstances at a multi-disciplinary child protection meeting (for example a case conference).

Include – traumatic damage or rupture of any abdominal viscera including deaths.

Exclude – external abdominal bruising alone and any accidental injury resulting in damage to abdominal viscera.

Methodology

The study has been conducted in conjunction with the BPSU. All Consultant Paediatricians across the UK and Ireland are asked to report cases of internal abdominal injury due to child abuse that they encounter, to the BPSU.

A questionnaire, which has been designed to collect information about the demographic details of the case child, mode of presentation and any previous child protection concerns prior to this particular injury is then dispatched. The exact nature of the internal abdominal injury, along with other associated injuries such as fractures, burns and bruises – particularly of the external abdominal wall, is enquired about. Information is sought on the diagnostic investigations undertaken, as well as the treatment and outcome in each case. Finally information about the family make-up (including information about the alleged perpetrator, where known) and also the child protection investigation and outcome is collected.

Working in collaboration with Professor David Yates in Manchester, who is conducting the 'UK Major Trauma Outcome Study', information about accidental internal abdominal injury in childhood has been obtained. This study has collected information for over a decade from over half of the A&E departments in the UK. Road traffic accidents and falls from over two metres are two of the commoner causes of accidental injury seen in this study, and details have been obtained regarding the pattern of internal abdominal organ injury seen as a result of these accidents. A comparison between these accidental injury patterns and those seen in the abused children has been made.

Ethical approval is in place for this study.

Analysis

Over the two-year period of case ascertainment, 76 notifications have been received. However, 22 notifications were made in error (for example, accidental injuries or external abdominal bruising alone), and 23 duplicate notifications have been received. At present we are still awaiting the return of five questionnaires.

The results presented here are based on an analysis of the 26 confirmed cases. The confirmed cases included nine deaths, of which seven were directly attributable to the internal abdominal injury.

The mean age of a case was 3years 3 months (range 1 month – 14 years) and 15 cases were female (58%).

In 14 cases (54%), small bowel injury (including duodenum) was reported and in nine of these rupture of small bowel / duodenum was evident. Of the nine deaths, six occurred in those cases with a small bowel injury. Other abdominal organs injured included the liver (five cases), the spleen 95 cases), the pancreas (four cases) and the kidney (two cases), with some children suffering injury to more than one organ.

In 10 (38%) cases, there were new or recent fractures found in association with the internal abdominal injury, and in six (23%) cases, NO external abdominal bruising was reported despite serious internal abdominal injury. In 17 cases (65%), child protection concerns were evident before the current episode of abuse resulting in internal abdominal injury.

When looking at the data collected by Professor Yates concerning accidental internal abdominal injury in children, of the 978 injured in a road traffic accident, only 76 (7.8%) had evidence of small bowel injury (including duodenum) and for 181 children who had fallen over two metres to sustain an internal abdominal injury, this injury was seen in only seven children (3.8%).

Conclusions

Internal abdominal injury due to child abuse seems to be a rare occurrence based on the small number of confirmed case notifications received over the two-year study period.

The findings to date suggest that small bowel injury (including duodenum) is the commonest internal abdominal injury resulting from abuse and these findings seem to mirror those reported in the USA by Ledbetter[6]. This type of injury is less frequently found in cases of accidental trauma, such as road traffic accidents. Although accidental trauma remains numerically the most common cause of small bowel injury, when such an injury is encountered without a history of major accidental trauma, this should raise suspicions that the injury is non-accidental.

The absence of external bruising despite the presence of serious internal abdominal injury in almost a quarter of our cases is similar to the figure reported by Ledbetter[6]. Children who present with abdominal symptoms or who are non-specifically unwell and shocked may have suffered an internal abdominal injury due to abuse yet have no obvious external markers. We would suggest that non-accidental injury should be considered as part of the differential diagnosis list in such cases (with CT scanning the diagnostic method of choice suggested in the literature[7]).

Mortality in our series seems to be high, as reported by others who have conducted research in this field [4]. Co-existent injury, particularly skeletal, seems to be common and should be looked for in all cases.

It is important to consider that only those cases in which the diagnosis is confirmed as child abuse at a case conference will be

received and this may lead to under-ascertainment. We are, however, reassured by the fact that duplicate notifications have been received, and we hope that this indicates that cases have been picked up through notification to the BPSU. At the time of submitting this annual report details concerning five case notifications were awaited.

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Progressive Intellectual and Neurological Deterioration (PIND) in Children

Key Points

- **Surveillance is planned until April 2004. We want to hear about all children with progressive intellectual and neurological deterioration even if you have already made a diagnosis! This is important because we want to ensure that ascertainment is as complete as possible.**
- **Six cases of variant Creutzfeldt-Jakob disease havebeen reported to the study since December 1998. Of these four have been classified as "definite" and two "probable" according to the National Creutzfeldt-Jakob Disease Surveillance Unit.**
- **Over the six-year study period *1504* children have been notified. *1073* cases have been discussed by an expert neurological advisory group of six paediatric neurologists. 625 have a definite diagnosis which is not vCJD, and these comprise *104* known degenerative conditions.**
- **There are districts with considerably higher rates of incidence of PIND. In some of these areas there are high consanguinity rates and a heterogeneous mixture of diagnoses.**

Background

Active prospective surveillance of UK children with progressive intellectual and neurological deterioration (PIND) commenced in May 1997. This is funded by the Department of Health, and carried out via the British Paediatric Surveillance Unit (BPSU) in coordination with the National Creutzfeldt-Jakob Disease Surveillance Unit in Edinburgh (NCJDSU) and the Health Protection Agency (HPA).

The main aim is to determine whether or not any children in this group have developed variant Creutzfeldt-Jakob disease (vCJD). Variant CJD had been described in patients as young as 16 years of age[1] and it therefore seemed possible that it could occur in younger children. There was a call for further epidemiological surveillance to investigate this issue[2]. The presentation of vCJD is not typical of classical CJD, and the clinical presentation of any cases in children is difficult to predict. The strategy is to detect suspected vCJD cases by looking at a broader group of conditions causing progressive intellectual and neurological deterioration in children (PIND). In this way, not only are vCJD cases detected, but also unique epidemiological data on a variety of PIND conditions are obtained[3].

The researchers use a detailed questionnaire to gather information via a telephone interview or site visit to review the case notes. An expert neurological advisory group consisting of six paediatric

neurologists supports the research team by meeting quarterly, discussing all newly notified anonymised cases, and classifying them according to study categories. There is further follow up of undiagnosed cases via the local paediatricians.

Objectives

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

Surveillance Period

Surveillance commenced in May 1997 and continues.

Case Definition

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

- Progressive deterioration for more than three months

With

- Loss of already attained intellectual/developmental abilities

And

- Development of abnormal neurological signs.

Excluding*:* Static intellectual loss, e.g. after encephalitis, head injury or near drowning.

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

- Metabolic disorders leading to neurological deterioration.
- Seizure disorders if associated with progressive deterioration.
- Children that have been diagnosed as having neuro-degenerative conditions but who have not yet developed symptoms.

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

Analysis

By the middle of March 2003 a total of 1504 children had been reported via the BPSU. There were 559 "No Cases" including those who did not fulfil the criteria for PIND, reporting errors, duplicate notifications etc. The 88 outstanding cases include 20 due for discussion at the May 2003 Expert Group meeting and 68 awaiting data collection. The remainder have been classified by the expert neurological advisory group into various study groups as shown in Figure 6.

Definite/Probable Cases of vCJD

Six cases of vCJD have been notified - the youngest was a girl aged 12 years at onset. The other five were three girls (two aged 14 years and one aged 13 years at onset) and two boys aged 15 years at onset. One child was notified in 1998, two in 1999, one in 2000 and two in 2001. All have died and neuropathology confirmed vCJD in four of them (classified as "definite" cases). Two has died without neuropathological investigation and one is still alive (classified as "probable" cases).

Figure 6 *PIND study – current status. Total reports 1504*

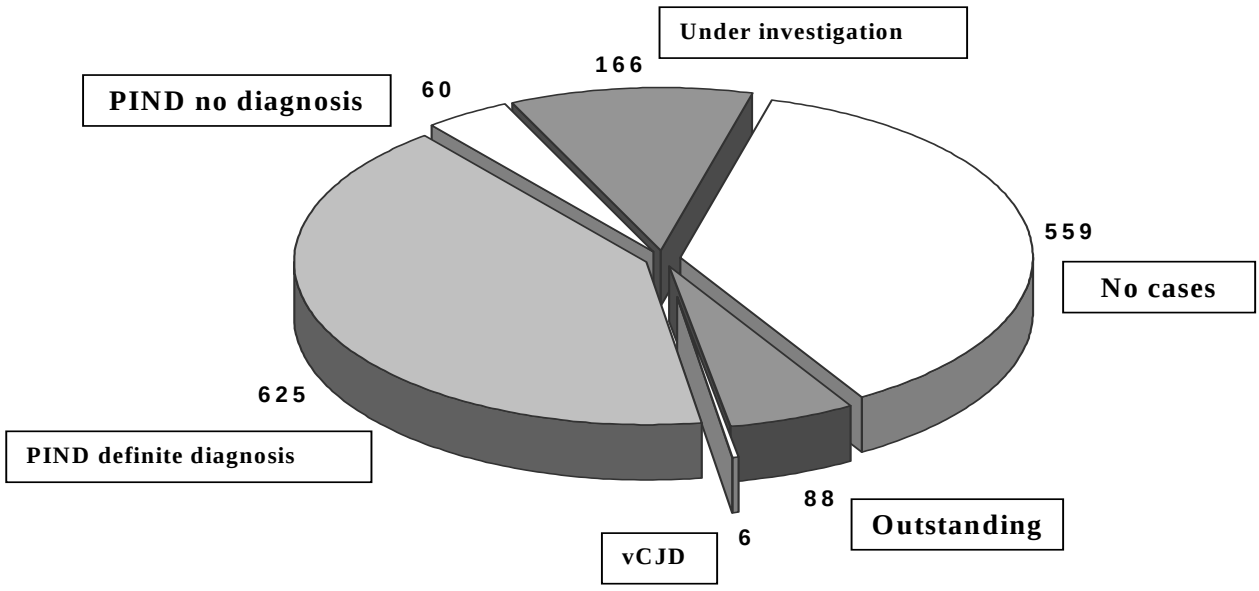


Figure 7 *Six most commonly reported PIND diagnoses*

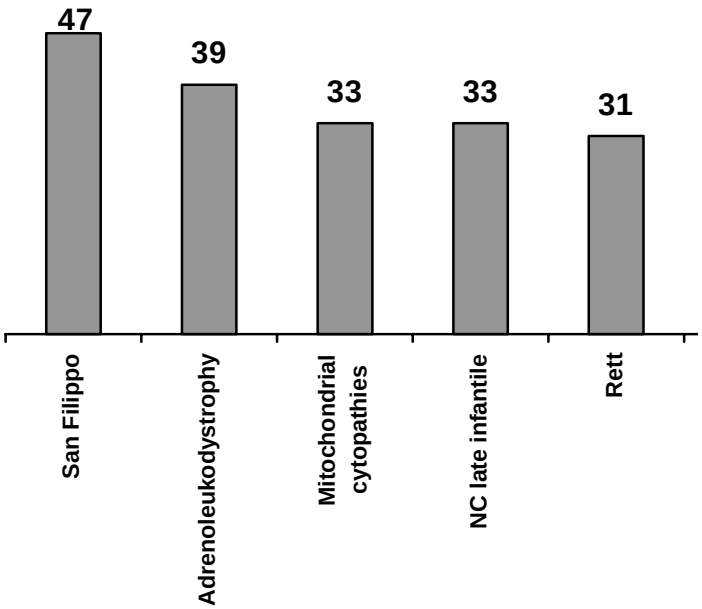
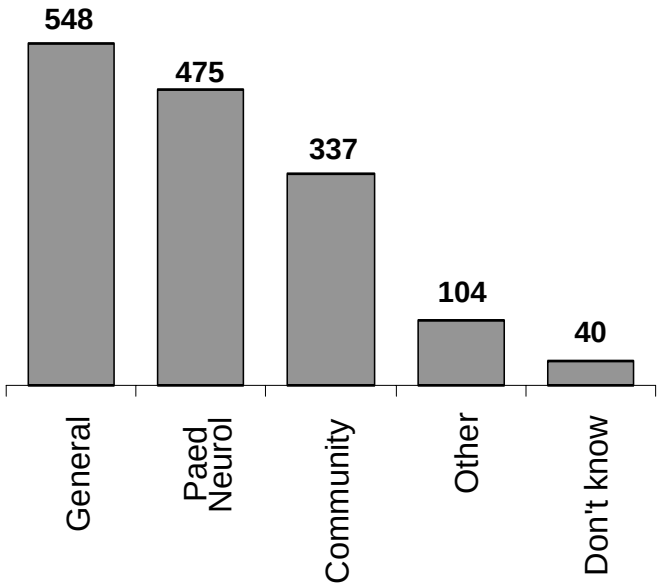


Figure 8 *Category of referring paediatrician*



Children who have definite PIND diagnoses other than vCJD

The study is producing unique population-based data on the causes of PIND. The majority of children with PIND have a known degenerative diagnosis or a likely underlying diagnosis which is not vCJD. In the 625 children with a confirmed diagnosis other than vCJD there were 104 different neurodegenerative conditions. The six most commonly occurring diagnoses are shown in Figure 7.

Variation in reporting by district

Geographical analysis by hospital of report and by residence reveals significant variations. A few hospitals have not reported any cases. There are some areas with considerably higher numbers of children with PIND. Yorkshire remains the highest reporting BPSU region (183 cases) with West Midlands (165 cases) followed by North East Thames (162 cases).

Variation in reporting by category of referring paediatrician

Most children were reported by general paediatricians followed by paediatric neurologists then community paediatricians (Fig 8).

Interim Conclusions

PIND surveillance has been running for six years now. Six cases of vCJD in children under 16 years of age at first presentation have been notified to the study. This includes four cases of definite vCJD and two cases of probable vCJD. One girl was age 12 years at onset, the youngest ever case of vCJD. There have been no other children with the clinical features of vCJD, however there is concern that more childhood cases may appear. Six years is a short time to perform surveillance for a disease about which there are still many unanswered questions - for example, the number of children who may be incubating vCJD, the length of the incubation period and the exact nature of transmission.

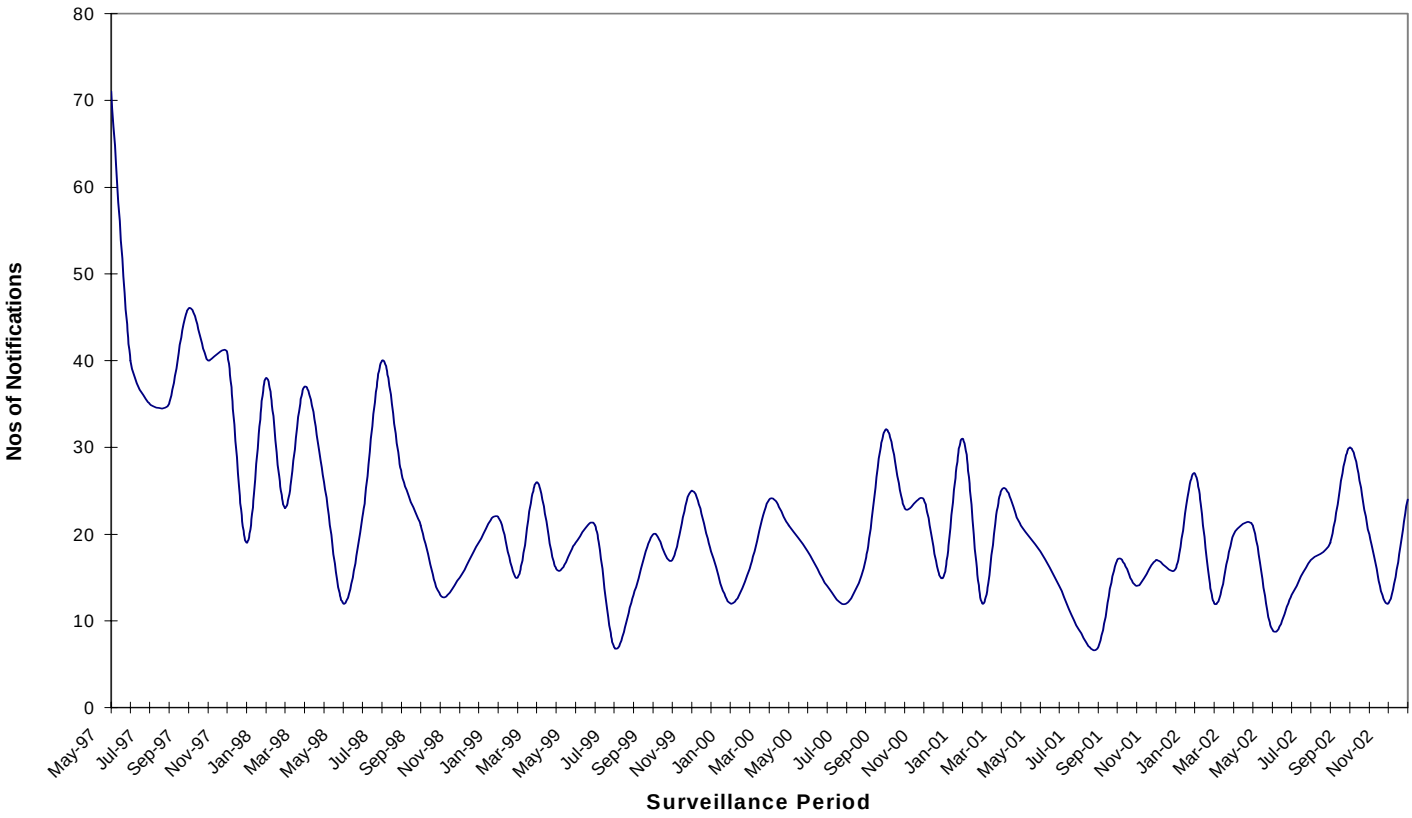
Acknowledgements

PIND surveillance is working very well and is yielding valuable information about the conditions that lead to PIND in children. Paediatricians are still responding enthusiastically with a median number of 20 notifications per month (Figure 9 overleaf). The PIND surveillance team is very grateful to the members of the expert neurological advisory group (Prof J. Aicardi, Dr P. Baxter, Dr S. Green, Prof. R. Robinson, Dr R. Surtees and Dr J. Wilson) for all their work in classifying cases and for the cooperation of UK paediatricians in support of this surveillance project.

Support Groups

1. Creutzfeldt-Jakob Disease Support Network, Birchwood, Heath Top, Ashley Heath, Market Drayton, TF9 4QR.
2. Batten Disease Family Association, c/o Heather House, Heather Drive, Tadley, Hampshire, RG26 4QR
3. The Society for Mucopolysaccharide Diseases, 46 Woodside Road, Amersham, HP6 6AJ.
4. Climb, (formerly the Research Trust for Metabolic Diseases in Children (RTMDC.), The Quadrangle, Crewe Hall, Weston Road, Crewe, CW2 6UR.
5. Adrenalleukodystrophy (ALD), ALD Family Support Trust, 30-32 Morley House, 320 Regent Street, London, W1R 5AB.

Figure 9 *Number of notifications each month*



6. Niemann Pick Disease Group, Kingslaw House, East Brae, East Wemyss, Fife KY1 4RS, Scotland.

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Severe complications of varicella (chickenpox) in hospitalised children

Key points

- **This study aims to estimate the annual incidence of complicated varicella in hospitalised children less than 16 years of age.**
- **91 cases have been reported in first six months of study and these are being followed up by questionnaire.**
- **All reporting clinicians wishing virological testing for severe cases of varicella are encouraged to submit throat swabs and/or vesicle fluid samples for molecular analysis at no charge.**

Background

Varicella zoster is an infectious virus, which causes varicella (chickenpox) on primary infection and herpes zoster upon subsequent reactivation. Approximately 90% of varicella cases occur in children less than 15 years of age with the highest incidence of infection in the one to four year age group[1,2]. Varicella is generally a mild disease in healthy children. Nevertheless, some severe complications may occur even in previously healthy children, including secondary bacterial infections, central nervous system manifestations, and death[3].

There are few data on complicated varicella cases in the UK. Routine hospital discharge records in the UK have been analysed previously [2,4], but cannot provide these data with sufficient detail or accuracy due to the problems inherent in retrospective studies.

The aim of this study is to estimate the burden of severe complications of varicella disease (chickenpox) in hospitalised children. Although almost all children with varicella are managed at home, it is acknowledged that there will be other children in hospital with varicella, either for specific treatment, or with a co-incidental condition, who will not meet the case definition. These patients are also an important group, but are too numerous to be included in the study.

A live-attenuated vaccine developed in Japan in the early 1970s has been shown to be safe and effective and is now recommended for routine use in all healthy children in several countries, including the United States and Canada[5]. The vaccine prevents varicella in 85% of immunised children, with 97% protection against moderately severe and severe disease [6].

There is currently no routine immunisation program against varicella in the UK, or the Republic of Ireland, although varicella vaccines are being introduced on a small-scale, named patient, basis for individuals considered to be at particularly high risk of complications and their seronegative close contacts. Decisions around the possible introduction of varicella vaccination are complex and it now seems doubtful whether the UK Joint Committee on Vaccination and Immunisation will recommend its administration to all healthy children in the near future. Nevertheless, data on varicella disease and its complications in UK and Ireland will contribute to the epidemiological and economic information available, and help to determine the future advisability of a universal or selective immunisation programme. If a vaccination programme were to be established the data would provide a baseline against which its impact can be evaluated.

Objectives

Primary

- To estimate the annual incidence of complicated varicella in hospitalised children less than 16 years of age.

Secondary

- characterise varicella complications;
- describe the characteristics (age, underlying medical conditions) of these children;
- estimate the annual financial cost of hospitalisation for severe varicella;
- estimate the annual mortality from varicella in children.

Surveillance period

November 2002 - November 2003 (inclusive).

Case definition

Any child less than 16 years hospitalised with complicated varicella, as defined by a list of clinical conditions*, or admitted to a paediatric ICU or HDU with varicella or one of its complications.

*Bacteraemia/septic shock; toxic shock syndrome/toxin-mediated disease; necrotising fasciitis; encephalitis; purpura fulminans/disseminated coagulopathy; pneumonia (abnormal x-ray); neonatal varicella; fulminant varicella; Reye's syndrome; ataxia; admitted into ICU/HDU; death due to varicella.

Analysis

Data has been collected since November 2002. In the first five months of surveillance (November 2002 to March 2003), 91case notifications have been sent to the Scottish Centre for Infection and Environmental Health through the BPSU. Follow-up questionnaires are sent out for all notifications, requesting further information on the patient, clinical features, underlying medical conditions, clinical outcome and length of hospital stay. Interim analysis will start at the end of April 2003 for the first six month period.

Virological testing

All reporting clinicians wishing virological testing for severe cases of varicella are encouraged to submit throat swabs and/or vesicle fluid samples for molecular analysis at no charge. Please contact Dr Judy Breuer, Consultant in Virology, St Barts and The London. Tel: 020 7 377 7141.

Funding

Scottish Centre for Infection and Environmental Health

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Suspected fatal adverse drug reactions in children

Key Points

- **This prospective study intends to document whether fatal adverse drug reactions (ADRs) are a problem in children in the UK.**
- **To date eight cases have been reported through the BPSU, four of which have been confirmed.**
- **A further 10 cases have been reported through the yellow card system.**

Background

The Yellow Card Scheme, set up in 1964,is the UK's spontaneous reporting scheme is the mainstay of drug safety monitoring in the UK. It is widely recognised that there is under-reporting of ADRs in adults and it is perceived that there may be greater under-reporting of suspected adverse drug reactions (ADRs) in children. Medicines in children are frequently prescribed "off-label" and therefore have not been formally evaluated for safety and efficacy in that age group. It is particularly important to report and detect potential drug safety issues in children. As a first step, this prospective study was intended to document whether fatal adverse drug reactions are a problem in children in the UK."

Objective

To study the frequency and nature of suspected adverse drug reactions with a fatal outcome in children below the age of 16 years.

Surveillance Period

June 2002 – June 2003 (inclusive).

Methodology

All cases meeting the case definition were identified using the BPSU Orange Card. Details of the case were sought through a written questionnaire. If necessary, a further follow-up letter was sent. The patient, family or other health professional involved with the care for the child were not contacted. A causality assessment will be undertaken[1]. An expert panel will be convened to discuss individual cases.

Case Definition

Any child below the age of 16 years with a suspected adverse drug reaction with a fatal outcome. ADRs include suspect reactions to vaccines. Importantly clinicians are also asked to report cases seen through the Medicines and Healthcare products Regulatory Agency (formerly the Medicines Control Agency) Yellow Card scheme.

Results

During the period 1 June 2002 to 31 December 2002, five reports of suspected fatal ADRs (and an additional three reports that were errors) have been received in this study. This includes one case (a duplicate), which was received on a Yellow Card the month earlier and one case in which the questionnaire has not been returned. The cases received are as follows:

- A case of cardiovascular collapse leading to arrest in a five week old premature infant following a dose of thyroxine for congenital hypothyroidism.
- A case of liver failure following the use of enalapril for heart failure in a teenager with pre-existing congenital heart disease.

- A case of exacerbation of chronic lung disease of prematurity in a 16-week-old infant, three weeks corrected age, following immunisation with Prevenar (streptococcal pneumoniae conjugate) vaccine and a study vaccine DT5aP-Hib-IPV (the duplicate case).
- A case of cardiorespiratory arrest in a 13-year-old following minor ENT surgery, the suspected drugs being isoflurane, suxamethonium, fentanyl and propofol.

A further three reports have been received since December 2002; clinical details are awaited.

During the same seven month period, 10 reports of suspected fatal ADRs were received through the Yellow Card scheme. Seven of these were reported by the Company. Three consultant paediatricians reported via the Yellow Card scheme and not through this BPSU study.

Conclusions

The response to this study has been disappointing. One of the cases received through this study was reported through the well-established Yellow Card scheme first and during the same seven month period, a total of 10 reports of suspected fatal ADRs were received through the Yellow Card scheme.

Possible reasons for this low response include:
- The number of ADR- related deaths in children is genuinely low.
- Paediatricians associate ADRs with the Yellow Card scheme
- The assumption of greater under-reporting by paediatricians may be incorrect.
- There may be an under-recognition of the role of ADRs in deaths in sick children

Funding

The Medicines and Healthcare products Regulatory Agency (formerly the Medicines Control Agency), UK

Reference

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Thrombosis in Childhood

Key Points

- **Study duration 25 months. has now closed to recruitment.**
- **Initial data collected on 268 episodes, 172 fitting study criteria.**
- **82.5% of cases reported were DVT/PE.**
- **Main risk factors were sepsis, immobility, central venous/femoral lines and malignancy.**
- **Overall mortality low (7%) 12 cases.**

Background

Symptomatic thrombotic events, venous and arterial, are rare in childhood, particularly after the neonatal period, and the incidence in the UK is unknown. A Canadian Registry of deep vein thrombosis/pulmonary embolism (DVT/PE) in children (age 1 month to 18 years)[1] prospectively identified 137 patients, giving an incidence of DVT/PE of 5.3/10,000 hospital admissions, or 0.07/10,000 children in Canada. Infants under one year of age and teenagers predominated (18% and 50% respectively) with an equal sex distribution. Two retrospective reviews report an incidence of clinically symptomatic DVT in children and PE in adolescents/young adults of 1.2 and 7.8 cases per 10,000 hospital admissions. Advances in tertiary care paediatrics with its accompanying increase in invasive procedures, and a growth in organ transplantation, may be contributing to an increase in incidence.

Current management decisions for children with thrombosis are directly extrapolated from treatment recommendations for adults with no further validation. To accept recommendations for adult patients as optimal management for paediatric patients, these two patient populations and their thrombotic problems have to have basic features in common. These parameters include the primary underlying disorder, the distribution of vessels involved, the interaction of anticoagulant and thrombolytic drugs with the haemostatic system, the pharmacokinetics of these drugs and the risk of serious complications of the disease and treatment. Available data suggests there are important differences.

DVT involves the upper system in between 26-36% of children (due to the use of central venous catheters) compared to 1-2% of DVT in adults. Idiopathic DVT is rare (4% in the Canadian Registry and 2% in the literature) in contrast to approximately 30% of adult DVT, and more than 95% of children with DVT/PE have one or more predisposing factors. The role of acquired and inherited thrombophilia in children remains unclear.

There have been no comparative studies evaluating the sensitivity and specificity of diagnostic procedures in children, and given the differences in the size and location of vessels involved, it is unlikely that the results from comparative studies in adults can

be extrapolated to children.

There is a profound effect of age on plasma concentration of coagulation proteins, with secondary effects on the regulation of thrombin and plasmin. This subsequently influences the pharmacokinetics of anticoagulants which strongly suggests that optimal therapy for children with thrombo-embolic disease and its complications may differ significantly from adults.

Objectives

- To determine the incidence and epidemiology of thrombosis in the UK in children aged between 1 month and 16 years.
- To determine which risk factors predispose to thrombosis in childhood, and in particular, the role of thrombophilia – both inherited and acquired.
- To determine current diagnostic and therapeutic practice for childhood thrombosis, and to assess if there is sufficient available information on which to develop management guidelines.

Surveillance Period

February 2001 – February 2003 (inclusive).

Case definition

Any child aged between one month (or 44 weeks post-conceptional age) and 16 years newly diagnosed with an objectively documented venous or arterial thrombosis.

Exclude: children with stroke whether this is arterial or due to sino-venous thrombosis.

Preliminary results

Three hundred and thirty-four thrombotic episodes have been reported during the 25 month duration of this study and data collection forms sent to reporting clinicians. Initial data have been collected on 268, with 172 fitting the study criteria. 96 (36%) were excluded because of duplicate reporting or non-fulfilment of the study criteria. Six-month follow up data are available on 96 cases.

Site of Thrombus: Of the 172 cases reported 142 (82.5%) were DVT/PE, 13 cases (7.6%) arterial thombosis, eight cases (4.6%) cardiac, and the remaining 5.3% were combined problems. Of the peripheral venous events, 66% occurred in the lower limbs and 28% in the upper limbs, jugular and subclavian veins.

Risk Factors: The main risk factors identified were sepsis, immobility or both (56%), central venous/femoral lines (43%), and malignancy (22%). Other risk factors included renal disease/ nephrotic syndrome, surgery, transplant and family history. In only 17 cases were no risk factors reported.

Diagnostic Investigations: Doppler ultrasound, echocardiogram, venogram, CT and MRI scans were the main method of diagnosis, with ultrasound being the most common at 66%. In 33% of cases more than one diagnostic investigation proved to be abnormal.

Management: Unfractionated Heparin or low molecular weight heparin for anticoagulation (LMWH) followed by Warfarin was the treatment of choice in 47% of cases. A further 37% received Heparin/LMWH alone. Of the patients with central venous/ femoral lines insitu 62% were removed. 13 patients received thrombolytic therapy and eight patients underwent surgical thrombectomy.

Outcome: 59 patients (34%) achieved complete resolution, 70 patients (41%) partial resolution, and 43 patients (25%) had either no resolution or outcome was "not known" at the time the forms were completed. However, the time between the thrombotic event and completion of the form may have a bearing on this figure. The six-month follow up mailing forms will give a more accurate picture of the incidence of complete resolution. Bleeding complications were noted in only 11 cases. Nine of these were minor, but major bleeds were reported, with subsequent death, in two cases. Although the cause of death in these two cases was primarily due to their underlying pathology, anticoagulation therapy may have contributed. The overall mortality for all patients reported was low at 7%.

Conclusions

Interim results demonstrate considerable heterogeneity in the events recorded and in current diagnostic and management strategies. Although these events are often associated with significant morbidity, mortality does appear to be low.

This study has now closed. For the study to provide accurate data on which to base future diagnostic and therapeutic practice, it is important to collect information on as many thrombotic episodes as possible. To this end all outstanding forms are being targeted to try to optimise the number of cases available for analysis.

The coordinators would like to thank all clinicians who have participated in this study and would ask for their continued support in completing six-monthly follow up data.

Funding

Local hospital research fund.

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Vitamin K deficiency bleeding

Key points

- **Seven cases have so far been identified over the course of the study.**
- **Four were early onset and three were late onset.**
- **Four had received no vitamin K because parental consent was withheld, two had oral prophylaxis.**
- **In four cases the birth unit's policy for vitamin K prophylaxis had not been followed, in all because of parental refusal or indecision.**
- **Comparing against the two previous BPSU surveys a significant fall in incidence has been seen.**

Background

The BPSU survey of Haemorrhagic Disease of the Newborn 1988-90 clearly demonstrated that the condition remains a cause of death and handicap which is preventable by vitamin K prophylaxis[1]. Intramuscular prophylaxis gave more reliable protection than oral in the doses then used. In 1992 wide publicity in the popular press has been given to studies suggesting a link between vitamin K prophylaxis administered to neonates and subsequent development of childhood cance[2]. Subsequent studies have given some reassurance but it may never be possible to exclude a 10% increase in risk. As a result, paediatricians have repeatedly reviewed their prophylaxis recommendations and many parents are anxious about the use of vitamin K in any form. More In 1996 Konakion MM Paediatric became licensed for oral prophylaxis and is increasingly used. There is no uniformity of practice and so continued surveillance for VKDB remains essential.

The first and second BPSU surveys of Vitamin K Deficiency Bleeding (VKDB) were carried out between 1989-90[1] and in 1993-4[3] and demonstrated that:

- VKDB was still occurring in the British Isles despite widespread use of vitamin K prophylaxis.
- VKDB is a significant cause of preventable mortality and morbidity.

Vitamin K is now given in four common but very different regimens. In 1993 one or two units gave no routine prophylaxis, some gave a single oral dose, some gave multiple oral doses and some gave intramuscular vitamin K to all infants[4]. The relative risk of bleeding in infancy is maximum in the first and minimum in the last of these groups with dramatic differences across the groups; babies given no prophylaxis (including those whose parents have refused it) are eighty times more likely to bleed than those given intramuscular prophylaxis[5]. Errors in administration of the planned regimen or parental refusals would tend to mask these differences[5].

Surveys of vitamin K prophylaxis in the United Kingdom in 1988 and 1993[4] showed an increase in the number of infants receiving prophylaxis orally and since that then there has been an increase in the number of infants receiving multiple oral prophylaxis regimens with Konakion K MM (Roche) or other preparation.

Unsuspected liver disease continues to be a high risk factor for VKDB[1,6].

Surveillance Period

January 2001-January 2003 (inclusive).

Research Questions

- Have the recent changes in vitamin K prophylaxis regimens, with the introduction of vitamin K MM in various dosages, altered the prevalence of VKDB?
- Do failures to achieve the planned prophylaxis regimen remain a major cause of morbidity?
- Do the newer regimens and preparations reduce the risk of VKDB when there is co-existing liver disease?
- When vitamin K is **NOT** given, is this because
  a) policy of the maternity unit?
  or b) parents chose not to follow recommended policy?
  or c) policy inadvertently not followed?
- Was there delay in presentation when the significance of apparently trivial warning was not appreciated?

Case definition

Any infant under 6 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.

NOTE: The same definition was used for "Haemorrhagic disease of the newborn" in the previous BPSU survey[1]. An Expert Committee convened at the request of the Department of Health and chaired by Professor David Hull agreed that the term "Haemorrhagic disease of the newborn" was potentially misleading - it did not mention vitamin K or exclude other causes of bleeding and it erroneously implied a condition confined to the newborn period and was sometimes confused with "Haemolytic Disease of the Newborn". The new term, Vitamin K Deficiency Bleeding, was agreed to be more informative and correct[7] and so has been adopted internationally and so will be used in this survey.

Please note that measurement of clotting parameters before the administration of blood products or vitamin K remains very important. This is particularly so in relation to agreed international criteria for diagnosis, which are essential in comparing data with other countries who have different regimens of prophylaxis.

Table 12 *Comparison of the 2001-02 VKDB study with previous studies*

Study Period (2 years)	Cases	Breast fed	No Vit K	Consent* Withheld	Oral Vit K	IM Vit K	Underlying Disease (liver)	ICH	Death
1988-90	27	24	19	Not asked	6	--	6 (6)	10	2
1993-94	32	25	10	4	16	2	14 (12)	10	--
2001-02	7**	6	4	4	2	1	2 (1)	1	--

* Consent for vitamin K prophylaxis withheld
** Final figure may be higher

IM = intramuscular *ICH = intracranial haemorrhage*

Analysis

The third 2-year BPSU study of vitamin K deficiency bleeding (VKDB) ended in January 2003. Following 39 notifications, 31 questionnaires have been returned; 13 have been classified as 'no case' and four were duplicates. In seven cases further information is awaited for classification; if unavailable they will be classified as 'no case'. The current total of confirmed cases is seven and brief details are summarised in Table 12, together with corresponding data from the two previous studies:

Discussion

The numbers of notifications and of questionnaires returned have been far smaller in the third than in the previous two studies. Whilst this could reflect waning interest in a subject studied twice before, we think this very unlikely - the subject of vitamin K prophylaxis still causes as much concern to parents and paediatricians as ever and the proportion of notifications classified as 'no case' remains high, implying a low threshold for notification of even dubious cases, despite the effort involved. Thus, while some data are still outstanding and the final figure of confirmed cases may rise, we are confident that there has been a significant fall in the incidence of VKDB and a corresponding fall in the mortality and morbidity from intracranial haemorrhage. What has brought about the change? Factors may include change in vitamin K prophylaxis (begun a survey of current practices has begun) and better surveillance for congenital liver disease.

Four babies presented at 2-7 (median 2) days. None had received vitamin K prophylaxis, in each case because parental consent was withheld; in all cases the local policy would have been for IM prophylaxis but (at least in three) for oral vitamin K to be offered if IM was refused. All the babies were born at term and were breastfed. Two suffered gastrointestinal bleeding (one in association with campylobacter infection), another presented with post-circumcision oozing. The fourth suffered a hypoglycaemic convulsion at two days and was later found to have a small extradural intracranial haemorrhage; it is postulated that the intracranial haemorrhage led to the poor breastfeeding and subsequent hypoglycaemia.

Three cases presented after seven days, so-called late VKBD. One "probably" received multiple oral doses of vitamin K, was solely breastfed and presented at 37 days with bruising of two days duration; jaundice was noted (total billirubin 118, conjugated 65 ìmol/L) and biliary atresia was later diagnosed. Another definitely received multiple oral doses of vitamin K and presented at eight weeks with bruising, six days after a nosebleed and five days after post-immunisation oozing; the baby had been breastfed and then changed to a soya milk formula, but still failed to thrive. Cystic fibrosis was diagnosed after presentation with VKDB. The third baby was born at 30 weeks, received intramuscular vitamin K 0.5 mg and was solely breastfed; at almost eight weeks spontaneous bruising was noted and the baby was brought to hospital immediately. No underlying disease was found.

Summary

The incidence, mortality and morbidity of VKDB are all lower in the third BPSU study than in the previous two; the reasons are yet unknown but may include changes in prophylaxis policies, better acceptance of prophylaxis and earlier investigation of prolonged jaundice / failure to thrive.

The importance of minor "warning bleeds" is again emphasised. Early identification of vitamin K deficiency may pre-empt life threatening intracranial haemorrhage; this should become well known amongst health professionals and parents alike.

It is noteworthy that in four of the seven cases parents refused vitamin K prophylaxis.

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6 New Studies 2003

Invasive fungal infection in very low birthweight infants

Background

Nosocomial invasive fungal infection, most commonly due to *Candida spp*., is an increasingly common cause of morbidity and mortality in preterm infants cared for in the neonatal intensive care setting[1, 2]. The increase in incidence over the past 20 years is likely to be due to the improved survival rates of very immature infants, and the invasive and intensive nature of the care that these infants need. The estimated incidence of invasive fungal infection in very low birth weight infants (VLBW: birth weight <1500 g) is about 2%[2,3]. In extremely low birth weight infants (birth weight <1000 g), the incidence has been estimated to be as high as 10%.[4] However, these estimates are based on limited case-series from tertiary centres in North America, and may have been affected by referral and ascertainment biases. Additional putative risk factors for invasive fungal infection include fungal colonisation, severe illness at birth, the use of multiple courses of antibiotics, the use of parenteral nutrition, the presence of a central venous catheter, and the use of H_2 antagonists[3].

In neonatal intensive care units, systemic candidal infection accounts for about 10% of all cases of sepsis diagnosed in infants more than 72 hours old. The estimated attributable mortality of about 25% is much higher than that associated with invasive bacterial infection[2,3]. The clinical presentation of invasive fungal and bacterial infection is similar. In addition to fungaemia, infants may present with pneumonia, meningitis, renal tract infection, ophthalmitis, osteomyelitis, endocarditis, and skin abscesses. Invasive fungal infection may present at an earlier age in extremely preterm infants (<26 weeks) compared with more mature VLBW infants[5]. The diagnosis may be delayed due to an inability to recover consistently the organism from blood, cerebro-spinal fluid (CSF), or urine[6]. A high index of suspicion and the use of additional laboratory and clinical tests, including echocardiography, retinal examination, and renal ultrasonography may be needed to confirm the suspected diagnosis.

Given the high mortality, and the difficulty in establishing an early diagnosis, there is a need to assess the effect of strategies to prevent invasive fungal infection in VLBW infants[7]. The evaluation of such measures would be assisted by the availability of national epidemiological data in an unselected population of VLBW infants. These data would:

- provide an estimate of incidence that is unaffected by referral bias (denominator: ISD/Birth counts)
- define the population most at risk (for example extremely preterm infants)
- describe the pattern of presentation.

This national surveillance study also aims to determine the outcome at 37 weeks post-conceptional age. This information may be important in the counselling of parents whose infants develop invasive fungal infection.

Surveillance Period

February 2003-February 2004 (13 months).

Case Definition

Live born VLBW infant with confirmed invasive fungal infection as determined by one or more of the following:

- culture from a sterile site:
- CSF
- blood (from peripheral sites, not from indwelling catheters)
- urine (obtained by sterile urethral catheterisation or supra-pubic bladder tap)
- bone or joint
- peritoneal or pleural space
- central venous line tip
- pathognomonic findings on ophthalmological examination
- pathognomonic findings on renal ultrasound examination
- autopsy diagnosis

Objectives

- What is the incidence of invasive fungal infection in very low birth weight infants?
- What are the patterns and clinical spectrum of presentation?
- What organisms are responsible (including anti-fungal resistance patterns)?
- What are the current treatment strategies?
- What are the short-term clinical outcomes?

Ethics Approval

This study has been approved by the Scottish MREC.

Funding

Departmental funds, and also by supported by an unrestricted educational grant from Pfizer Ltd.

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Severe hyperbilirubinaemia in the newborn

Background

During the past decade, encephalopathy due to severe hyperbilirubinaemia in the newborn has been reported with increasing frequency in the United States and Europe[1 2]. This potentially preventable condition causes substantial mortality, and neurodevelopmental morbidity in survivors. Previously it had been encountered mainly in babies with severe Rhesus isoimmunisation[3 4], and had declined in frequency thanks to effective prevention and treatment of this condition. The reappearance of bilirubin encephalopathy has been ascribed to earlier discharge of newborn babies, and to a more relaxed approach to the management of jaundice in well term babies, particularly those breast fed[5]. These trends have occurred in Britain[6], but there have been no systematic studies reporting an increased incidence of severe hyperbilirubinaemia, nor of bilirubin encephalopathy, in Britain. The primary objective of this study is to determine the incidence of severe hyperbilirubinaemia in the newborn in the United Kingdom and the Republic of Ireland.

Surveillance Period

June 2003-June 2004 (13 months).

Objectives

- What is the annual incidence of severe unconjugated hyperbilirubinaemia during the first month of life in the United Kingdom and Republic of Ireland?
- What known risk factors and demographic features are associated with severe hyperbilirubinaemia in the newborn?
- What are the consequences of severe hyperbilirubinaemia in this group of babies?

Case Definition

Severe hyperbilirubinaemia (unconjugated serum bilirubin > 510 micromols/L) in the first month of life.

Ethical Approval

The London MREC has approved the study.

Funding

Wirral Hospital NHS Trust and the Wirral Hospital Neonatal Endowment Fund will fund the study jointly.

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Langerhans cell histiocytosis

Background

Langerhans Cell Histiocytosis (LCH), previously known as Histiocytosis X, is a disease in which cells ('LCH cells') accumulate with other immune cells in various parts of the body and cause tissue damage. LCH can affect skin, bone, pituitary gland, lungs, intestines, liver, spleen, bone marrow and brain. The disease is more common in children than adults and may be severe in young children when several organs are affected[1].

The cause of LCH is unknown. It may be triggered by an unusual reaction of the immune system to something commonly found in the environment. It is not a known infection or a cancer and, although there may be a more than one patient in certain families[2], it is usually not hereditary.

Around 10-20% of patients, usually infants, die. In other patients the disease usually burns itself out, but there may be long term sequelae due to damage caused by the disease process[3,4].

Diagnosis: This is usually confirmed following a biopsy of affected tissue. To determine the extent of disease and subsequent treatment plan, blood tests, imaging and sometimes liver or bone marrow biopsy are required. The disorder may initially present to general paediatricians, oncologists, dermatologists, orthopaedic surgeons, haematologists, ENT specialists, endocrinologists, gastro-enterologists or neurosurgeons.

Treatment: In some cases the disease regresses spontaneously regardless of treatment. For others, conservative surgery, steroid therapy or chemotherapy will be required. However, in some cases the disease is unresponsive and can progress despite extreme measures including bone marrow transplant. Clinical trials are now in progress via the Histiocyte Society, which also provides advice on diagnosis and management.

Epidemiology: It is estimated that one in 200,000 children are affected each year. Over 75% of cases occur before the age of 10 years. However, epidemiological data are sparse and only one national incidence estimate (5.4 per million) has been reported for Denmark, during the 1980's[5]. It is estimated that there are between 50 -100 new cases per year in children in the UK which has a childhood population of around 12 million, and possibly an equal number of cases in adults.

There are few epidemiological studies of LCH. Two large case-control studies have been reported from the USA, in which risk factors for the development of LCH were investigated. In the first study, LCH was associated with maternal urinary tract infection and with feeding problems, use of medication and blood transfusions in the index case. No associations were found between childhood environmental exposures and LCH[6]. In the second study postnatal exposures associated with multisystem LCH included infections, diarrhoea and vomiting and medication use. LCH was strongly associated with thyroid disease in the proband and in other members of the family[7]. No unifying hypothesis regarding risk factors for LCH has emerged from these studies.

LCH has been associated with childhood cancer, including both leukaemias and solid tumours[8].

Surveillance Period

June 2003-June 2004 in the first instance.

Objectives

- to describe the epidemiology of LCH in the UK and RoI. In particular, to:
    - i) to describe the incidence of LCH in boys and girls by age and extent of disease at diagnosis
    - ii) to assess the frequency of familial LCH
    - iii) to document patterns of presentation e.g. interval between the onset of symptoms and diagnosis
    - iv) to study variation between ethnic groups
    - v) to determine whether or not there are differences in LCH incidence within each country, to describe regional differences in incidence rate and to assess geographic variation e.g. north/south or urban/rural.

Case Definition

Children of any age newly diagnosed with either (a) or (b)

a) biopsy-proven LCH; lesional cells (LCH cells) must contain Birbeck granules or be CD1a positive or S100 positive with characteristic H&E morphology. Central review of histopathology slides is available
b) Lytic bone lesion or pituitary/hypothalamic abnormality with the characteristics of LCH but not biopsied whether
    - i) because clinical features suggest spontaneous resolution

    or
    - ii) because the risk of the biopsy procedure in view of the location on the lesion (eg cervical vertebra, pituitary mass), is considered too great

Clinical features of LCH include: otherwise unexplained bone pain with/without overlying soft tissue swelling; proptosis; recurrent otitis with otorrhoea; rash resembling seborrhoeic dermatitis on scalp and in flexures, but resistant to topical treatments; interstitial pneumonitis; unexplained colitis; sclerosing cholangitis; diabetes insipidus; unexplained hypothalamic-pituitary dysfunction.

Methodology

Case ascertainment will be primarily through the BPSU. However, dermatologists, pathologists, orthopaedic surgeons and haematologists will also be circulated directly by the investigators. An expert committee will monitor the project and provide support to reporting clinicians.

On reporting a case the clinician will be sent a questionnaire seeking information on presentation and referral. Minimum identifier data will be requested in order to exclude duplication. Information will be sought on socio-demographic characteristics, family history, ante-natal and birth history, presenting symptoms, referral patterns / timing, and treatment. Follow up information about each child will be collected one year after notification and will address treatment received, relapses/ recurrences of disease, sequelae and outcome at follow up.

The families will not be contacted. Measures will be taken to ensure confidentiality.

Ethical Approval

The London MREC has approved this study.

Funding

Histiocytosis Research Trust.

Support Group

C/o Contact a Family, 209-211 City Road, London, EC1V 1JN. Tel. 020 7608 8700.

References

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Professor L Parker, Paediatric Epidemiologist, Newcastle University, Sir James Spence Institute, Royal Victoria Infirmary, Newcastle upon Tyne, NE1 4LP. Tel: 0191 202 3023 (Direct line). Fax: 0191 202 3060. Email: Louise.Parker@ncl.ac.uk

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Neonatal herpes simplex virus (HSV) infection

Background

Neonatal herpes simplex virus (HSV) infection is a rare but potentially devastating condition. It can follow primary or recurrent maternal infection, or be acquired postnatally through direct contact with infected secretions. Transplacental transmission is unusual, and perinatal infection is usually acquired during vaginal delivery through an infected birth canal.

The relative contribution of primary and recurrent maternal infection to neonatal disease, the prevalence of neonatal infection and the proportion of neonatal disease associated with HSV-1 and HSV-2 varies between countries. Primary maternal infection close to term is estimated to lead to neonatal infection in about one third of cases, and to be about 10 times more likely than a recurrence of maternal infection to result in neonatal infection.

Prior infection with HSV-1 is partially protective against the acquisition of HSV-2. Although oral infection is predominantly associated with HSV-1, and genital infection with HSV-2, there is considerable crossover, and genital HSV-1 is common, and becoming more so. However, the majority of women who have had genital HSV are probably not aware of the fact. Both primary infection and reactivation can be asymptomatic.

Neonatal presentation and outcome

Infants who present with disease *localised* to the skin, eye and/ or mouth (SEM) have the best prognosis and death is unusual, although impairment can occur, possibly associated with sub-clinical CNS infection. Those who present with acute *disseminated* HSV infection have multiple organ involvement, including the liver, lungs, gastrointestinal tract and CNS; the likelihood of death is high, and nearly all survivors have severe handicap. Infants with *encephalitis confined* to the CNS often

present late, and may not develop skin lesions; the mortality rate is around 50%, and the long-term prognosis is poor for those who survive.

Early diagnosis is vital in all cases since antiviral therapy can significantly affect outcome.

Surveillance of neonatal HSV was previously undertaken through the BPSU in 1986-1991. The estimated prevalence of infection was then 1.65/100,000 (CI 1.3-2.0/100,00). HSV-1 and HSV-2 were reported in equal proportions, but in one third of cases the virus was not typed. Approximately equal numbers of infants presented with localised, disseminated and CNS infection. Given the rarity of the condition, and the observation that most infants were born to women with no prior history of infection, it was considered at that time that antenatal screening was not justified.

There have been important changes in the demographic profile of the British population in the last 15 years, and there is increasing concern about the prevalence of sexually transmitted diseases; these factors could also have contributed to an increase in the incidence of neonatal HSV in the British Isles.

Surveillance Period

Autumn 2003 – Autumn 2004.

Objectives

- To estimate the current birth incidence of neonatal herpes infection (HSV-1 and HSV-2) in the British Isles.
- To explore the presentation of neonatal infection, and management of diagnosed cases.
- To assess morbidity and mortality at one year follow up through the notifying paediatrician.
- To compare findings with the 1986-91 BPSU cohort, and with INoPSU studies currently being undertaken in Australia and Canada.

Surveillance Case definition

Any infant under one month

(a) with a diagnosis of HSV infection, based on virus culture, or serology, or PCR,

or

(b) treated with antiviral drugs for suspected HSV infection

Analytic case definition

Confirmed case of neonatal HSV:

1. Virus culture, specific IgM, PCR confirming HSV infection on a specimen taken in the first four weeks of life, or
2. Typical clinical manifestations with maternal infection confirmed by either seroconversion or virus isolation around the time of delivery

Suspected case of neonatal HSV:

3. Typical clinical manifestations and treated with antiviral drugs for suspected HSV infection.

Funding

Departmental Funds.

Ethical Approval

To be sought.

Support Group

The Herpes Viruses Association, 41 North Road, London N7 9DP. Helpline tel: 020 7609 9061

References

1. Neonatal herpes simplex virus infection in the British Isles. Tookey P, Peckham C. *Paediatric and Perinatal Epidemiology* 1996, **10**: 432-442
2. IHMF. Herpesvirus infections in pregnancy. Recommendations from the IHMF Management Strategies Workshop and 7th Annual Meeting. Eds Pass RF, Weber T, Whitley RJ.1999 (Available from www.ihmf.org)

Dr P Tookey, Professor C Peckham, Mr R Lynn. Centre for Paediatric Epidemiology and Biostatistics, Institute of Child Health, 30 Guilford Street, London WC1N 1EH. Tel: 020 7905 2604. Fax: 020 7905 2381. E-mail P.tookey@ich.ucl.ac.uk.

7 International Network of Paediatric Surveillance Units (INoPSU)

Background

Following the success of the BPSU, the same methodology was adopted and adapted in the 1990s to other countries whose paediatric services are amenable to an active surveillance approach. Within Europe this led in 1992 to units in the Netherlands and Germany and 1994 in Switzerland. The European paediatric surveillance units then met and communicated regularly in order to discuss surveillance protocols.

The European initiative was also the stimulus for the development in 1992 of an Australian unit and later the Malaysian unit (1994) to be followed more recently by Units in Canada (1996), Papua New Guinea (1996), New Zealand and Latvia (1997) and Portugal (2001). Greece/Cyprus (2003) is the latest country to develop a surveillance unit. Wales (1995) and Republic of Ireland (1997) developed surveillance units using a similar methodology to the BPSU, though they are concentrating on less rare disorders.

Through the use of active ascertainment the thirteen units provide an efficient, effective framework for case-finding for investigators who wish to study rare conditions in children. These include infections, infection-related conditions, vaccine-preventable diseases, congenital and inherited (genetic) diseases, unusual injuries or therapies and rare complications of common diseases. The units frequently encourage, facilitate or elicit studies but only occasionally undertake research themselves.

The director of the Australian unit, Professor Elizabeth Elliott, keeps in contact with those of units in Papua New Guinea, New Zealand and Malaysia. Given the existence of at least ten national paediatric surveillance units undertaking similar work and this level of informal contact it was accepted by the units that the time has come to formalise these links into a network.

In 1996 the proposal to form an International Network of Paediatric Surveillance Units (INoPSU) was accepted in principle by all units existing at that time. Now all the units contact each other for results, sharing of protocols, putting researchers in touch with each other and a common international report is shared as part of national reports.

The Network was formed in August 1998 at a meeting of the 10 units expressing a desire to link with each other. This took place at the 22nd International Congress of Paediatrics in Amsterdam, The Netherlands. The first INoPSU conference was held in June 2000 in Ottawa, Canada sponsored by Health Canada and was attended by representatives of most of the existing units.

The mission of INoPSU is the advancement of knowledge of uncommon childhood infections and disorders and the participation of paediatricians in surveillance on a national and international basis so as to achieve a series of benefits. A document known as the Amsterdam-Ottawa Note detailing the functions and structure of the network has been agreed and has been posted on the INoPSU website at http://www.inopsu.com.

Following the first INoPSU conference in 2000 the Welsh Paediatric Surveillance Unit was accepted into the Network. The Portuguese and Irish Units were accepted as full members of the Network in 2002 (see Table 13 opposite) whilst the newly formed Greece/Cyprus Unit has been accepted as an affiliate until which time it can meet the criteria for full membership. The British Ophthalmological Surveillance Unit continues as an associate member.

Professor Elliot will continue as convenor of the INoPSU secretariat until April 2004 with the BPSU acting as server.

Following the second INoPSU conference held in 2002 at York University UK, it was agreed a further conference would be held in Portugal in April 2004. A summary of the meeting was included in the 16th Annual Report.

Details on the activities of each surveillance unit is available form their respective website and also from the INoPSU website.

Table 13 *INoPSU Units*

Country	Child population (10^6 aged 0-15 yrs)	Established	Respondents	Reply paid	Response Rate	Fee for study?
Australia	3.9	1992	1042	Yes	96%[1]	Yes
UK/Rep of Ireland	12.8	1986	2005	No	93%	Yes
Canada	6.3	1996	2294	Yes	83%	Yes
Germany	12.0	1992	468*	No	98%	Yes
Latvia	0.4	1996	22	No	70%	No
Malaysia	7.7	1994	395	Yes	75%	No
Netherlands	2.9	1992	445	Yes	87%[3]	Yes
Papua New Guinea	2.0	1996	40	Yes	79%	No
New Zealand	0.8	1997	165	Yes	95%[2]	No
Switzerland	1.3	1995	40*	Yes	100%	No
Wales	0.65	1994	119	No	100%	No
Republic of Ireland	1.0	1996	135	Yes	85%	Yes
Portugal	1.8	2001	1500	Yes	30%	Yes

[1] 538 (52%) from a total 1042 clinicians reported to the APSU by email in 2001.
[2] Respondents reply either by reply-paid card (30%) or to an email (70%) depending on their preference. Telephone notification of AFP is also requested.
[3] Since January 2002, approximately 30% of paediatricians have received their card via email.

Contact details for INoPSU Units are overleaf.

INoPSU Unit contact details

Australian Paediatric Surveillance Unit

A/Prof Elizabeth Elliott (Director), Ms Donna Rose (Scientific Co-ordinator)
APSU, c/o The Children's Hospital at Westmead, Locked Bag 4001, Westmead, NSW 2145, Australia.
Tel: ++61 2 9845 3005/2200
E-mail: apsu@chw.edu.au
Website: www.apsu.inopsu.com

British Paediatric Surveillance Unit

Mr R Lynn, Professor M Preece, 50 Hallam Street, London W1W 6DE. Tel: 00 44 207 3075671
E-mail: bpsu@rcpch.ac.uk .Website: http://bpsu.inopsu.com

Canadian Paediatric Surveillance Program

Andrea Medaglia, CPSP Senior Coordinator, 100-2204 Walkley Rd., Ottawa ON K1G 4G8
Tel: 613-526-9397 ext. 239
E-mail: cpsp@cps.ca
Website: www.cps.ca/english/CPSP/CPSP.htm

German Paediatric Surveillance Unit

Professor R Von Kries, Institute for Social Paediatrics and Adolescent Medicine, Ludwig-Maximilians University Munich, Germany Tel: 0089 71009 314
E-mail: ag.epi@lrz.uni-muenchen.de
Website: www-public.rz.uni-duesseldorf.de/~esped/rahmen.html

Greece/Cyprus Paediatric Surveillance Unit

Dr C Hadjichristodoulou, Papanastasiou 12, Agaleo, 12242, Athens, Greece.
Tel: 00 301 (0)6423058
E-mail: hadjich@ath.forthnet.gr

Latvian Paediatric Surveillance Unit

Professor E Bikis, Skolas Street 3-105, Riga, Latvia.
Tel: 00 371 760571
E-mail: aspedlat@com.latnet.lv

Malaysian Paediatric Surveillance Unit

Dr Rowani Modi, Department of Paediatric, School Of Medical Sciences, Universiti Sains Malaysia Health Campus, 16150, Kubang Kerian, Kelantan, Malaysia
Tel: 00 609 7663000 ext 3633 Fax: 00 609 7653370
Website: http://www.kck.usm.my/suhaila/mpsu/index.htm#

Netherlands Paediatric Surveillance Unit

Dr Rob Rodrigues Pereira, TNO Prevention and Health, Postbus 2215, 2301 CE Leiden, Netherlands.
Tel: 00 3171.5181838
E-mail r.pereira@pg.tno.nl

New Zealand Paediatric Surveillance Unit

Professor B Taylor, Dr N Dickson, Ms M Carter, University of Otago, Dept of Women's and Children's Health, Dunedin School of Medicine, PO Box 913, Dunedin, New Zealand.
Tel: 00 64 3 474 7825
E-mail: nzpsu@stonebow.otago.ac.nz.

Papua New Guinea Surveillance Unit

Dr G Ogle Co-ordinator PNG Paediatric Surveillance Unit. C/o HOPE Worldwide (PNG),
POBox 3478, Boroko, NCD, Papua New Guinea
Tel: 00 675 325 6901
E-mail: Graham_Ogle@hopeww.org or hopepng@datec.com.pg
Website: www.hopeww.org/Where/png/png5.htm

Portugal Paediatric Surveillance Unit

Dr M Coelho, Co-ordinator, Portuguese Paediatric Society, Daniel Virella, R. Amílcar Cabral, 15 - r/c I 1750-018 Lisbon, Portugal
Tel: 00351 21 757 46 80 / 9990
E-mail: coelhom@mail.telepac.pt or dvirella@oninet.pt.
Website: http://www.spp.pt/ingl/index.html

Republic of Ireland Paediatric Surveillance Unit

Professor D Gill, Children's Hospital, Temple Street, Dublin 1, ROI.
Tel: 003531 8741751 Fax: 003531 8748355 E-mail:gilld@iol.ie

Switzerland Paediatric Surveillance unit

Dr. HP Zimmermann, Swiss Paediatric Surveillance Unit, Swiss Federal, Office of Public Health, 3003 Bern, Switzerland.
Tel: 0041 31 323 8710 Fax: 0041 31 323 8795
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Welsh Paediatric Surveillance Unit

Dr. J Morgan, Co-ordinator, Children's Centre, Royal Glamorgan Hospital, Llantrisant, Wales CF72 8XR
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Appendix A Completed Studies 1986-2002

By mid-2002 the BPSU had completed forty-five studies. Information about these studies has been included in previous annual reports of the BPSU, which are available from the BPSU office. The studies, principal investigators and definitive papers are listed below. For addresses see the list at the end of this report.

X-linked anhydrotic ectodermal dysplasia
Completed: June 1986 - August 1986
Investigator: Dr A Clarke
Published paper: X-linked anhydrotic ectodermal dysplasia. Clarke D. BPSU 2nd Annual Report 1987. BPSU London

Haemorrhagic shock encephalopathy syndrome
Completed: June 1986 - December 1988
Investigator: Dr S Hall
Published Paper: Haemorrhagic Shock Encephalopathy Syndrome in the British Isles. Bacon CJ, Hall SM.
Arch. Dis. Child. 1992; **67**: 985-993

Haemolytic uraemic syndrome I
Completed: June 1986 - December 1989
Investigators: Dr C M Taylor, Dr D Milford, Dr S Hall
Published paper: Haemolytic Uraemic Syndrome in the British Isles 1985-88; Association with Verocytotoxin-Producing *E.coli*: Milford DV, Taylor CM, Guttridge B, Hall SM, Rowe B, Kleanthous H. *Arch. Dis. Child.* 1990; **65**: 716-72

Kawasaki disease
Completed: June 1986 - December 1992
Investigator: Dr S Hall
Published Paper: Kawasaki Disease in the British Isles. A survey of management: Dhillon R, Newton L, Rudd PT, Hall SM
*Arch. Dis. Child.*1993. **69**: 631-638
Kawasaki disease - Lessons for Britain: Bissenden JG, Hall SM. *BMJ.* 1990; **300**: 1025-1026

Lowe syndrome
Completed June 1986 - February 1988
Investigator: Dr C McKeown
Published Paper: Lowe Syndrome. McKeown C. BPSU 2nd Annual Report. 1987. BPSU London

Neonatal herpes
Completed: June 1986 - Dec 1991
Investigators: Ms PA Tookey, Professor C S Peckham, Dr R Dinwiddie
Published Paper: Neonatal herpes simplex virus infection in the British Isles: Tookey P, Peckham CS.
Paediatr Perinat Epidemiol 1997; **10**: 432-442

Insulin dependent diabetes in under fifteens
Completed: January 1988 - December 1988
Investigator: Professor J D Baum
Published paper: Incidence of Insulin Dependent Diabetes in Children Aged Under 15 Years in the British Isles During 1988: Metcalfe MA, Baum JD. *BM J* 1991; **302**: 443-7

Drowning and near drowning
Completed: January 1988 - December 1989
Investigators: Professor J Sibert, Dr A Kemp
Published Paper: Drowning and near drowning in children in the United Kingdom: lessons for prevention: Kemp A, Sibert JR. *BMJ*. 1992; **306**: 291-297
Outcome in Children Who Nearly Drown: a British Isles Study: Kemp AM, Sibert JR. *BMJ* 1991; **302**: 931-933

Haemorrhagic disease of the newborn
Completed: March 1988 - February 1990
Investigators: Dr AW McNinch, Dr H Tripp
Published paper: Haemorrhagic Disease of the Newborn in the British Isles: a two year prospective study: McNinch AW, Tripp JH. *BMJ* 1991; **303**: 1105-1109

Galactosaemia
Completed: Jan 1988 - Sept 1991
Investigators: Mrs A Green, Dr J Holton, Dr M Honeyman, Professor J Leonard
Published paper: Galactosaemia, Results of the British Paediatric Surveillance Study 1988-90: Honeyman MM, Green A, Holton JB, Leonard JV. *Arch. Dis. Child.* 1993; **69**: 339-341

Congenital toxoplasmosis
Completed: June 1989 - May 1990
Investigator: Dr S Hall
Published paper: Screening for Toxoplasmosis during Pregnancy: Peckham CS, Logan S. *Arch. Dis. Child*. 1993; **68**: 3-5

Higher order births
Completed: January 1989 - December 1989
Investigator: Professor M Levene
Published paper: Higher multiple births and the modern management of infertility in Britain. For the British Association of Perinatal Medicine: Levene MI, Wild J, Steer P.
Br J Obst Gynaecol 1992; **99**: 607-613

Acute rheumatic fever
Completed: January 1990 - December 1990
Investigators: Dr C Boyd-Scobie, Dr S Hall Acute Rheumatic Fever. Boyd-Scobie, Hall S.
Published paper: BPSU 5th Annual Report. BPSU London 1990

Rett syndrome
Completed: April 1990 - June 1990
Investigator: Dr A Kerr
Published paper: Rett Syndrome: British Longitudinal Study (1982-1990) and 1990 Survey. In Mental Retardation and Medical Care. Roosendaal JJ (ed.). Uitgeverij Kerckebosch, Zeist 1991

Measles, mumps, rubella-meningococcal meningitis
Completed: Jan 1990 - Dec 1991
Investigator: Dr N Begg
Published paper: Meningoencephalitis associated with MMR vaccine: Maguire HC, Begg NT, Handford SC.
Communicable Disease Report 1991; 1 (**6**): R57-R59

Chemistry set poisoning
Completed: Jan 1991 - April 1992
Investigator: Dr E Mucklow
Published paper: Chemistry Set Poisoning: Mucklow ES. *Internat. Journ. Clin. Pract.* 1997; **51.5**: 321-23

Acute flaccid paralysis
Completed: July 1991- June 1994
Investigator: Dr N Begg
Published paper: Polio Eradication: Surveillance Implications for the United Kingdom: Salisbury DM, Ramsay ME, White JM, Brown DW. *Infect. Dis*. 1997; **175 (Suppl 1)**: S156-9

Androgen insensitivity syndrome
Completed: Sept 1991 - Aug 1993
Investigator: Professor IA Hughes
Published paper: Androgen Insensitivity syndrome: a survey of diagnostic procedures and management in the UK. Viner RM, Teoh Y, Williams DM, Patterson MN, Hughes IA.
Arch Dis Child. 1997; **77**: 305-309

Long term parenteral nutrition
Completed: Feb 1992 - April 1992
Investigators: Professor D Candy, Professor E Ross,
Dr S P Devane
Published paper: Survey of children on long term parenteral nutrition, UK and Eire 1992. Devane S P. Abstract RCPCH Scientific Meeting 1993

Insulin dependent diabetes in under fives
Completed Jan 1992 - Dec 1992
Investigators: Professor JD Baum, Ms E Wadsworth
Published Paper: Insulin dependent diabetes in children under five: incidence and ascertainment validation for 1992.
BMJ 1995; **67**: 700-703
Dermatoglyphics, fetal growth and insulin dependent diabetes in children under five: Shield JP, Wadsworth EJ, Hobbs K, Baum JD. *Arch. Dis. Child*. 1995 **72(2)**: 159-60

Juvenile dermatomyositis
Completed: June 1992 - Dec 1993
Investigators: Dr D Symmons, Dr A Sills
Published Paper: The incidence of juvenile dermatomyositis: results from a nationwide study: Symmons DP, Sills JA, Davis SM. Br *J Rheumatol* 1995; **34**: 732-736

Congenital dislocation of the hip
Completed April 1993 - July 1993
Investigators: Dr C Dezateux , Dr S Godward
Published Paper: A national survey of screening for congenital dislocation of the hip: Dezateux C, Godward S. *Arch. Dis. Child*. 1996; **74**: 445-448
Screening for congenital dislocation of the hip in the newborn and young infants. Dezateux C, Godward S. Edinburgh 1997; Churchill Livingstone

Haemophagocytic Lymphohistiocytosis
Completed September 1991 - August 1994
Investigators; Professor S Strobel, Dr M Taylor, Dr J Pritchard
Published Paper: 10th BPSU Annual Report 1995/96. BPSU London 1995

Non-accidental poisoning/ Munchausen syndrome by proxy
Completed September 1992- August 1994
Investigator: Dr P Davis, Professor J Sibert,
Professor SR Meadow, Dr R McClure
Published paper: The epidemiology of Munchausen Syndrome by Proxy, Non-accidental poisoning and Non-accidental suffocation: McClure RJ, Davis PM, Meadow SR, Sibert JR. *Arch. Dis. Child.* 1996; **75**: 57-61

Neonatal necrotising enterocolitis
Completed October 1993 - October 1994
Investigators: Professor A Lucas, Ms R Abbott
Published Paper: Neonatal necrotising enterocolitis: 11th BPSU Annual Report 1996/7. London 1997

Vitamin K deficiency bleeding II
Completed January 1993 - December 1994
Investigators: Dr A McNinch, Dr J Tripp
Published paper: Vitamin K Deficiency Bleeding, 9th BPSU Annual Report 1993/94. London 1994

Biliary Atresia
Completed March 1993 - February 1995
Investigators: Dr JP McKiernan, Dr D Kelly, Dr AJ Baker
Published paper: The frequency and outcome of biliary atresia in the UK and Ireland McKiernan JP, Baker AJ, Kelly D
Lancet 2000; **355**: 25-29

Transient and permanent neonatal diabetes
Completed: July 1994- August 1995
Investigator: Dr J Shield, Professor JD Baum, Ms E Wadsworth
Published paper: Aetiopathology and genetic basis of neonatal diabetes: Shield JP, Gardner RJ, Wadsworth EJ, Whiteford ML, James RS, Robinson DO, Baum JD, Temple IK.
Arch. Dis. Child. 1997; **76**: F39-F42

Adverse neonatal outcomes of delivery or labour in water
Completed: April 1994- April 1996
Investigators: Ms P Tookey, Dr R Gilbert
Published paper: Labour and birth in water in England and Wales. Aldernice F, Renfrew M, Marchant S, Ashurst H, et al. *BMJ* 1995; **310**: 837
Perinatal mortality and morbidity among babies delivered in water: surveillance study and postal survey Gilbert R E and Tookey P A. *BMJ* 1999; **319**: 483-487.

Congenital syphilis
Completed: July 1993 - July 1996
Investigators: Dr A Nicoll, Dr T Lissauer
Published paper: Syphilis in pregnant women and their children in the United Kingdom: results from national clinician reporting surveys: Hurtig A-K, Nicoll A, Carne C, Lissauer T et al**.** *BMJ*. 1998; **317**: 1617-9

Congenital cataract
Completed**:** Oct 1995 - Oct 1996
Investigator: Dr J Rahi
Published paper: National cross sectional study of detection of congenital and infantile cataract in the United Kingdom: role of childhood screening and surveillance: Rahi JS, Dezateux C, *BMJ* 1999; **318**: 362-365
Capture-recapture analysis of ascertainment by active surveillance in the British Congenital Cataract Study: Rahi JS, Dezateux C, for the British Congenital Cataract Interest Group*:* *Invest. Ophthalmol. Vis. Sci.* 1999; **40**: 236-239

Medium chain acyl-CoA dehydrogenase
Completed: March 1994 - March 1996
Investigators: Dr R J Pollitt, Prof J Leonad
Published paper: Prospective surveillance study of medium-chain CoA dehydrogenase deficiency in the United Kingdom: Pollitt RJ, Leonard JV. *Arch. Dis. Child.* 1998; **79**: 116-119
Neonatal screening for inborn errors of metabolism: cost, yield and outcome: Pollitt R J, Green A, McCabe CJ, et al. Health Technology Assessment Report 1997

Pyroxidine dependent seizures
Completed**:** Sept 1995 - Oct 1996
Investigator: Dr P Baxter
Published paper: Epidemiology of pyridoxine dependent and pyridoxine responsive seizures in the UK. Baxter P.
Arch Dis Child. 1999; **81(5)**:431-3.

Neonatal Meningitis
Completed:July 1996 - Dec 1997
Investigators: Dr D Holt, Mrs S Halkett .
Published Paper: Neonatal meningitis in England and Wales: 10 years on. Holt DE, Halket S, de Louvois J, Harvey D.
Arch Dis Child Fetal Ed 2001; **84**:F85-F89

Cerebral oedema and death following diabetic ketoacidosis
Completed: October 1995 - September 1998
Investigators: Dr J Edge, Dr M Hawkins
Published Paper: The risk and outcome if cerebral oedema developing during diabetic ketoacidosis. Edge JA,Hawkins MA, Winter DL, Dunger DB. *Arch Dis Child* 200; **85**: 16-22

Hepatitis C virus (HCV) infection
Completed: March 1997 - March 1999
Investigators: Dr D Gibb, Ms P Neave
Published paper: Active surveillance of hepatitis C infection in the UK and Ireland. Gibb DM, Neave PE, Tookey PA, Ramsay M, Harris H, Balogun K, Goldberg D, Mieli-Vergani G, Kelly D.
Arch Dis Child. 2000; Apr;**82(4)**: 286-91

Congenital brachial palsy
Completed: March 1998- March 1999
Investigators: Dr G Evans-Jones, Mr S P J Kay, Professor M Weindling
Published Paper: Congenital brachial palsy: incidence, causes, and outcome in the United Kingdom and Republic of Ireland. Evans-Jones G, Kay S P J, Weindling A M, Cranny G, Ward A, Bradshaw A, Hernon C.
Arch. Dis. Child. Fetal Neonatal Ed. 2003; **88**: F185-F189

Subdural haematoma and effusion
Completed: April 1998- April 1999
Investigators: Dr C Hobbs, Dr J Wynne, Dr A M Childs
Published Paper: 14th BPSU Annual Report 1999/00. London 2000

Inflammatory bowel disease in under 20 year olds
Completed: June 1998-June 1999
Investigators: Professor B Sandhu, Dr A Sawczenko
Published Paper: Prospective survey of childhood inflammatory bowel disease in the British Isles Sawczenko A, Sandhu B K Logan, R F A, Jenkins H, Taylor C J, Mian S, Lynn R.
Lancet 2001; **357**: 1095-96

Fatal/Severe allergic reactions to food ingestion
Completed: March 1998- February 2000
Investigators: Dr A Colver, Dr A Cant, Dr C MacDougal
Published Paper: How dangerous is food allergy in childhood? The incidence of severe and fatal allergic reactions across the UK and Ireland. Macdougall CF, Cant AJ, Colver AF.
Arch Dis Child 2002; **86**: 236–239

Invasive Haemophilus influenzae infection
Completed: October 1992-October 2000
Investigators: Dr P Heath, Dr J McVernon, Professor R Booy
Published Paper: Vaccine failures after primary immunisation with Haemophilus influenza type-b comjugate vaccine without booster. Booy R, Heath PT, Slack MPE, Begg, N, Moxon ER, *Lancet*,1997; **349**:1197-202

Haemolytic Uraemic Syndrome II
Completed: February 1997- February 2001
Investigatosr: Dr M Taylor, Dr D Milford, Dr B Adak, Mr R Lynn, Dr M Locking, Dr S O'Brien
Published Paper: 15th BPSU Annual Report 2000/01. London 2001

Group B Streptococcal Disease
Completed: March 2000 - March 2001
Investigator: Dr P Heath
Published Paper: 15th BPSU Annual Report 2000/01. London 2001

Reye's Syndrome
Completed: June 1986 - June 2001
Investigators: Dr S Hall, Mr R Lynn
Published Paper: 15th Annual Report 2000/01. London 2001

Subacute Sclerosing Panencephalitis
Completed: June 1986 - June 2001
Investigator: Dr E Miler
Published Paper: 15th Annual Report 2000/01. London 2001

Encephalitis in Early Childhood (2 months – 3 years)
Completed: October 1998 – September 2001
Investigators: Dr K Ward, Professor E Ross
Published Paper: 16th Annual Report 2000/01. London 2002

Appendix B Published papers 2002-3

How dangerous is food allergy in childhood? The incidence of severe and fatal allergic reactions across the UK and Ireland. Macdougall CF, Cant AJ, Colver AF.
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Education and debate: Consent, confidentiality, and the threat to public health surveillance Commentary: Don't waive consent lightly involve the public**.** Verity C, Nicoll A.
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Congenital rubella: down but not out. Tookey P.
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No seasonality in month of birth of inflammatory bowel disease cases: a prospective population based study of British under 20 year olds. Card TR, Sawczenko A, Sandhu BK, Logan RFA.
Gut 2002; **51**: 814-815

MMR vaccine: review of benefits and risks. Miller E.
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Evaluation of the specificity and sensitivity of indirect immunoflourescence tests for IgG to human herpesviruses-6 and -7. Ward KN, Couto Parada X, Passas J, Thiruchelvam AD.
Journ Virol Meth. 2002 **106**: 107-113

Hib vaccination in infants born prematurely**.** Heath P T, Booy R, McVernon J, Bowen-Morris J, Griffiths H, Slack M P E, Moloney A C, Ramsay M E, Moxon E R
Arch Dis Child. 2003; **88**: 206-210

Congenital brachial palsy: incidence, causes, and outcome in the United Kingdom and Republic of Ireland. Evans-Jones G, Kay S P J, Weindling A M, Cranny G, Ward A, Bradshaw A, Hernon C. *Arch. Dis. Child. Fetal Neonatal Ed***.** 2003; **88:**F185-F189

Immunologic memory in *Haemophilus influenzae* type b conjugate vaccine failure. McVernon J, Johnson P D R, Pollard A J, Slack M P E, Moxon E R.
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Presenting features of inflammatory bowel disease in Great Britain and Ireland. Sawczenko A, Sandhu BK. *Arch Dis Child*. (2003) (in press)

Appendix C Presentations 2002-2003

RCPCH Annual Scientific Meetings 2002 and 2003

The BPSU study of bilary atresia: outcome after 8 years: McKiernan PJ, Baker AJ, Mieli-Vergani G, Kelly D. York, April 2003. *Arch Dis Child* 2003; **88** (Suppl 1): A13

Internal abdominal injury due to child abuse – findings of the first year of a BPSU study. Barnes M, Sibert J, Norton CA, Kemp AM. York 2003 *Arch Dis Child* 2003; **88** (Suppl 1): A33

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Why is mother-to-child transmission of HIV infection still occurring in the UK and Ireland? Reported births 1998-2002. Tookey PA, Masters J, York, April 2003 (poster). *Arch Dis Child* 2003; **88** (Suppl 1): A55

Changes in vertically acquired paediatric HIV in UK and Ireland over calendar time. Doerholt K, Duong T, Sharland M, Tookey P, Masters J, Gibb DM on behalf of CHIPS and NSHPC. York, April 2003. *Arch Dis Child* 2003; **88** (Suppl 1): A56

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Vitamin K deficiency bleeding - international surveillance findings. Von Kries R. York 2002

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The Canadian and British perspectives of paediatric intellectual and neurological deterioration; are the results comparable? Grenier D, Doherty J, Medaglia A. York 2002

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Haemophilus b vaccination strategies - is their need for a booster? McVernon J.

Is there any danger associated with MMR vaccination? Miller E.

Reducing the risk of mother to child transmission of HIV worldwide. Newell M-L.

Is inflammatory bowel disease on the increase? Sandhu B.

Cerebral oedema and diabetic ketoacidosis. Muirhead S. York.

vCJD in UK children - implications for the world. Verity C.

European Organisation for Rare Diseases - A parental support perspective. Youngs C.

Other Conferences & Meetings

Surveillance of Haemolytic Uraemic Syndrome in the UK and Ireland (1997-2001) Using the BPSU methodology. Adak GK, Lynn RM, Taylor CM, Smith HR, O'Brien SJ, Locking M, Coia JE, Reily WJ. World VTEC Conference. Edinburgh June 2003.

"What Causes Progressive Intellectual and Neurological Deterioration (PIND) in Children over 12 years old?" Verity C. British Paediatric Neurology Association Annual Meeting, Liverpool. 10-12 January 2003.

"Are children in the UK developing vCJD? A national surveillance study of children with progressive intellectual and neurological deterioriation." Review: Verity C. 55th Annual Scientific Meeting of the Paediatric Society of New Zealand. 27 November 2002.

"Are UK children in the UK developing variant CJD? A National Surveillance Study of Children with Progressive Intellectual and Neurological Deterioration." Verity C. American Academy for Cerebral Palsy and Developmental Medicine 2002 Annual Meeting12-14 September 2002.

Effects of ART on morbidity and mortality of UK and Irish HIV infected children (Abstract TuPeC4730). Gibb DM, Duong T, McGee L, Sharland M, Tookey PA. 14th International AIDS Conference, Barcelona, July 2002.

Internal Abdominal injuries in children under 14 years. Sibert J. Welsh Paediatric Society Spring scientific meeting. Llandudno May 2002.

Group B streptococcal disease in infants < 90 days of age: a surveillance study. Heath P. European Society of Paediatric Infectious Diseases. May 2002.

Interim Results of the BPSU childhood encephalitis survey. Ward K. Liverpool Paediatric and NorthWest Epidemiology Clubs. Liverpool 2002.

Interim results of the British Isles-wide Childhood Encephalitis Survey. Ward K. Oswaldo Cruz Foundation, Rio de Janeiro, Brasilia 2002.

HHV-6 AND -7 diagnosis and its relevance to measles notification. Ward K. Oswaldo Cruz Foundation, Rio de Janeiro, Brasilia 2002.

"Wide variation in neurodegenerative disease across the UK: findings from the national study of Progressive Intellectual and Neurological Deterioration (PIND) in children." Devereux G. British Paediatric Neurology Association Annual Meeting, Newcastle upon Tyne16-18 January 2002.

MMR: a cause of autism and inflammatory bowel disease. Miller E. Workshop on Safety of Vaccines. Leuven, Belgium. February 2002.

Relationship between presenting symptoms, site of disease activity, and height/weight Z Score at diagnosis of Crohn's disease in children aged < 16 years. Sawczenko A, Sandhu BK, Logan RFA. British Society for Paediatric Gastroenterology, Hepatology and Nutrition 2002.

No seasonality in month of birth of inflammatory bowel disease cases: a prospective population based study of British under 20 year olds Card TR, Sawczenko A, Sandhu BK, Logan RFA. British Society for Gastroenterology 2002.

"Is Alpers' syndrome likely to be confused with vCJD? Findings from the BPSU study of Progressive Intellectual and Neurological Deterioration in children."Poster: Water Naudé J. The British Paediatric Neurology Association Annual Meeting16-18 January 2002.